A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX, an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients With End-Stage Renal Disease on Hemodialysis

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ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

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IONIS"

Statistical Analysis Plan

ISIS 416858-CSS

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Date: May 30, 2019

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Statistical Analysis Plan Signature Page

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court Carlsbad, CA 92010

Compound Name: ISIS 416858

Protocol: ISIS 416858-CSS

Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Phannacokinetics, and Pharmacodynamics of Multiple Doses ofISIS 416858 (IONIS-FXfaxan Antisense Inhibitor of Factor **XI),** Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Protocol Version: 14 June 2018 (Protocol Amendment l)

Signature: [redacted] Date: [redacted]

Jonis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Signature: [redacted] Date: [redacted]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 9201 0

Signature: [redacted] Date: [redacted]

[redacted]
Jonis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Signature: [redacted] Date: [redacted]

[redacted]
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AF	atrial fibrillation
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCo-4hr	area under the plasma concentration-time curve from time zero to 4 hours
AUCo-24hr	area under the plasma concentration-time curve from time zero to 24 hours
BP	blood pressure
BUN	blood urea nitrogen
	maximum concentration
CRNMB	clinically relevant non-major bleeding
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ESRD	end-stage renal disease
FLRs	Flu-like reactions
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	heart rate
HRL	Hemostasis Reference Laboratory
hr, hrs	hour(s)
ICH	International Conference on Harmonization
INR	international nonnalized ratio
ISIS 416858	antisense inhibitor of Factor XI
IXRS	automated randomization system

Kg	Kilogram
LCRIS	local cutaneous reaction at injection site
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
MRL	Medpace Reference Laboratories
PD	phannacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QI	25th percentile
Q3	75th percentile
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(!y)
Study Drug	ISIS 416858 or placebo
TEAE	treatment emergent adverse event
Tmax	time to maximal concentration
ULN	upper limit of normal
VR	ventricular rate
WBC	white blood cell
WHO	World Health Organization

List of Modifications:

The following modifications have been made to SAP, version 1.0, dated August 20, 2018.

Section	Title	Change
1.3.5	Platelet Function Testing	Details ofBCH data added.
2.1	General Overview of Procedures	Blood centers of Wisconsin data added.
2.5.2	Laboratory Data	Clarification of data availability of immunogenicity
3.1.1	General Statistical Methods	visit windows added
3.1.4	Planned Interim Analysis	Added details that no unblinding interim analyses were conducted until final database lock.
3.3.3.3	Bleeding	Added details on minor bleeding summary.

1 INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

1.1 Study Overview

This is a Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study in end-stage renal disease (ESRD) subjects receiving hemodialysis at least 3 times per week for a minimum of 9 hours per week. Subjects will be stratified based on the diagnosis of documented atrial fibrillation (AF) at Screening (Yes/No), enrolled in PK substudy (Yes/No), enrolled in Platelet substudy (Yes/No), and then subjects will be randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive treatment with Study Drug (either ISIS 416858 or placebo).

Cohort A: 200 mg ISIS 416858 or placebo SC (3:1)

Cohort B: 250 mg ISIS 416858 or placebo SC (3:1)

Cohort C: 300 mg ISIS 416858 or placebo SC (3:1)

All cohorts will consist of up to 4-week screening period for procedures and a 26-week treatment period followed by a 12-week post-treatment evaluation period.

Approximately 204 subjects are planned to be enrolled in parallel in this study.

1.2 Objectives

1.2.1 Primary Objectives

To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ISIS 416858 (200, 250, and 300 mg once weekly) as compared to placebo as assessed by FXI activity reduction in ESRD patients on hemodialysis; [redacted]

1.2.2 Exploratory Objectives

To evaluate the incidence of myocardial infarction **(MI),** stroke, systemic embolism, and cardiovascular mortality.

1.3 Planned Method of Analysis

1.3.J Safety and Tolerability Outcomes

The primary safety outcome is the combination of major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) during the treatment period (or early study termination).

The safety and tolerability of ISIS 416858 will be accessed by determining the incidence and severity of adverse events (AEs) and will be evaluated by reviewing:

- AEs (including venous thrombocmbolism (VTE) and bleeding events)
- Vital signs and weight
- ECG
- Physical examination
- Clinical laboratory tests
- Coagulation parameters
- Use of concomitant medications including transfusions

1.3.2 Pharmacodynamic Outcomes

- Change from baseline in FXI antigen and activity
- Change from baseline in activated partial thromboplastin time (aPTT)
- The extent and frequency of clotting on the dialysis filters and circuit

1.3.3 Exploratory Outcomes

- Incidence of myocardial infarction **(MI),** stroke, systemic embolism, and cardiovascular mortality

1.3.4 Other Study Outcomes and Evaluations

- Dialysis adequacy (Urea Reduction Ratio and single pool Kt/v), changes in dialysis prescription (vascular access, time on dialysis, dry weight)
- PK

1.3.5 Platelet Function Testing

For the subgroup of subjects evaluated for platelet function and/or activation, an analysis of pre- and post-treatment results with ISIS 416858 may be conducted overtime and compared to treatment with placebo

1.4 Randomization & Treatment Allocation

Subjects will be randomized on Study Day 1 after all screening assessments have been completed and after the Investigator has verified that they are eligible. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

All subjects will be randomized using an automated system (IXRS). Subjects will be stratified based on the diagnosis of documented atrial fibrillation (AF) at Screening (Yes/No), enrolled in PK substudy (Yes/No), enrolled in Platelet substudy (Yes/No), and then subjects will be randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive treatment with Study Drug (either ISIS 416858 or placebo).

1.5 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

1.6 Data Monitoring

1.6.1 Safety Data Monitoring

Safety data will be monitored as indicated in the ISIS 416858-CSS Medical Monitoring Plan with monthly or more frequent reviews during the treatment and follow-up periods by the Sponsor Medical Monitor (or appropriately qualified designee) and PPD Medical Monitor (or appropriately qualified designee) throughout the study. Safety data to be reviewed will include selected chemistries, hematology, coagulation, ECG, vital signs and adverse events.

1.7 Data Management

An eCRF utilizing an Electronic Data Capture (EDC) application will be used for this Study.

I.7.1 Case Report Form Data

BioClinica (or designee) is responsible for creating the EDC data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. lonis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data arc corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

1.7.2 Laboratory Data

Jonis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets. Data from BCH may be stored in an Excel spreadsheet.

Immunogenicity results will be available after final database lock.

2.5.3 Pliarmacoki11etic Data and Immunogenicity (IM) Data

Jonis Pharmaceuticals, Inc. is responsible for the management and review of the PK plasma concentration data and IM data. This process involves reviewing the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The PK and IM data are not stored in the EDC system.

2 ANALYTICAL PLAN

2.1 General Overview of Analyses

2.1.J General Statistical Methods

Descriptive summary statistics including number of patients, mean, standard deviation, median, and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

PK parameters will be summarized using number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

All analyses and tabulations will be performed using SAS® Version 9.2 or higher and Phoenix/WinNonlin version 6.1 or higher on a PC platform.

A separate analysis for on-treatment period might be provided if deemed necessary.

Pooled groups:

Patients who are placebo-treated will be pooled and analyzed as a single placebo group. Patients who are ISIS 416858-treated may be pooled and summarized as the ISIS 416858 total group.

Baseline definition:

Unless otherwise specified, baseline for all safety laboratory results will be defined as the last non-missing measurement prior to the first dose. For post-dialysis Blood Urea Nitrogen (BUN) measures for Urea Reduction Ratio (URR) determination, post-dialysis baseline will be defined as the last non-missing post-dialysis measurement prior to the first dose

Analytical visits:

All post-baseline data will be summarized according lo the visit windows in the table below. For patients who have multiple visits within a window, the average will be used in the summary for continuous variable and the worst case result will be used for categorical variable.

Table I Visit window for Clotting

Analysis visit	Visit window
Screening	<1
Baseline	last non-missing measurement prior to the first dose
Day8	[2, 11]
Day 15	[12, 21]
Day29	(22, 35]
Day43	[36, 49]
Day 57	[50, 63]
Day71	[64, 77]
Day 85	[78, 91]
Day99	(92, 105]

Day 113	[106, 116)
Day 120	[117, 126)
Day 134	(127, 140)
Day 148	(141, 154)
Day 162	[155, 168)
Day 176	[169, 182]
Day 190	(183, 196]
Day 204	[197,210]
Day 218	[2I1, 224]
Day 232	[225, 238]
Day 246	(239, 252]
Day 260	[253, 266]

Table 2 Visit window for Vital Signs

Analysis visit	Visit window
Baseline	last non-missing measurement prior to the first dose
Day 5	(2, 6)
Day8	[7, 9]
Day 12	[10, 13]
Day 15	[14, 17]
Day22	[18,25)
Day29	[26, 32)
Day36	[33, 39)
Day43	[40, 46]
Day 50	[47, 53]
Day 57	[54, 60]
Day64	[61, 67]
Day71	[68, 74]
Day78	[75, 81)

Day85	[82, 88]
Day92	[89, 95]
Day99	[96, 102]
Day 106	[103, 109]
Day 113	[110, 116]
Day 120	[117, 123]
Day 127	[124, 130]
Day 134	[131, 137]
Day 141	[138, 144]
Day 148	[145, 151]
Day 155	[152, 158)
Day 162	[159, 165]
Day 169	[166, 172]
Day 176	[173, 182]
Day 190	[183, 196)
Day 204	[197,210]
Day 218	[211,224]
Day 232	[225,238]
Day 246	[239, 252]
Day260	[253, 266]

Table 3 Visit window for Electrocardiogram

Analysis visit	Visit window
Baseline	last non-missing measurement prior to the first dose
Day29	[2, 53]
Day78	[54, 126]
Day 176	[127,217]
Day260	[218,273]

Table 4 Visit window for Chemistry panel, Hematology, and Coagulation Panel

Analysis visit	Visit window
Baseline	last non-missing measurement prior to the first dose
Day5	(2, 8]
Day 12	(9, 13]
Day 15	[14, 18]
Day22	[19, 25)
Day29	[26, 32]
Day36	[33, 42]
Day 50	[43, 56]
Day64	[57, 70]
Day78	(71,84]
Day92	[85, 98]
Day 106	[99, 112]
Day 120	[113, 126]
Day 134	[127, 140]
Day 148	**(141,** 154]
Day 162	[155, 168]
Day 176	[169, 182]
Day 190	[183, 196]
Day 204	[197,210]
Day 218	[211, 224]
Day 232	[225, 238]
Day 246	[239, 252]
Day 260	[253, 266]

Table 5 Visit window for Blood Urea Nitrogen, Post-Dialysis BUN, Urea Reduction Ratio

Analysis visit	Visit window

Baseline	last non-missing measurement prior to the first dose
Day36	[2, 49]
Day64	[50, 77]
Day92	[78, 105]
Day 120	[106,133]
Day 148	(134, 161]
Day 176	[162, 189]
Day 204	[190, 217]
Day 232	[218,245]
Day260	[246, 273]

Table 6 Visit window for Inflammatory Markers

Analysis visit	Visit window
Baseline	last non-missing measurement prior to the first dose
Day 15	[2, 21]
Day29	[22, 39]
Day50	[40, 63]
Day78	[64, 91]
Day 106	[92, 119]
Day 134	[120, 147]
Day 162	[148, 168]
Day 176	[169, 189]
Day 204	[190,217]
Day 232	[218, 245]
Day 260	[246,273]

2.J.2 Populations

The following populations will be used in this study, and any exclusion of patients from the populations will be documented and decided upon by appropriate medical, clinical, data management, and statistical personnel at Ionis Pharmaceuticals prior to unblinding.

Intent-to-Treat Population (ITT)

All subjects randomized who have received at least 1 dose of Study Drug (ISIS 416858 or placebo). Results will be summarized under the treatment to which patients were randomized.

Per Protocol Population (PPS):

All subjects who are randomized without missing more than 2 doses during the first 12 weeks or more than 5 doses over the 26-week Treatment Period and who do not have any major protocol violations that would affect the interpretation or integrity of the study results.

Safety Population:

AH subjects randomized who have received at least I dose of Study Drug. Results for Cohorts A and B will be summarized under the treatment to which patients received.

Atrial Fibrillation (AF) Substudy population:

All randomized subjects who were reported at baseline as having a documented history of atrial fibrillation and have received at least 1 dose of Study Drug (ISIS 416858 or placebo).

PK Substudy Population:

All randomized subjects who participated in the PK subgroup and have received at least 1 dose of active Study Drug (ISIS 416858) and had at least 1 PK sample collected and analyzed with evaluable results for ISIS 416858 concentration.

PK Population:

All randomized subjects who have received at least 1 dose of active Study Drug (ISIS 416858) and had at least 1 PK sample collected and analyzed with evaluable results for ISIS 416858 concentration.

Platelet Function/Activation Substudy Population:

All subjects who participated in the Platelets Function/Activation substudy by having at least I evaluable sample assessed for flow cytometry and have received at least 1 dose of active Study Drug (ISIS 416858 or placebo).

In addition to the above analysis populations, it is recognized that some data displays will be provided for "All Screened" and "Screening Failures" patients.

2.1.3 Sample Size Co11sideration

The sample size was selected based on prior experience to ensure that the safety, tolerability and PK/PD relationships will be adequately assessed while minimizing unnecessary patient exposure. There is no statistical rationale for the selected sample size.

2.1.4 Planned Interim Analysis

No interim analysis is planned. However, during the study, an unblinded primary database lock analysis may be conducted after an patients complete the treatment period to assess the safety and PK/PD, and exploratory efficacy of the results. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study. All the post-baseline coagulation panel data and unblinded interim analysis will be conducted by unblinded team members including a clinician and biostatistician who will not be associated with the direct conduct of the study after the unblinding occurs with interim analysis. The individuals involved in the unblinded interim analysis will be identified and docwnented at the time of unblinded interim analysis according to lonis SOP.

The Investigator, study staff, patients, blinded monitors, and members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study.

2.1.5 Incomplete or Missing Data

In general, missing data values will not be imputed. Incomplete data handling rules will be described in the specified section if needed.

2.2 Demographic and Baseline Characteristics

Demographic and Baseline characteristics (including dialysis and ESRD disease characteristics e.g., age, gender, ethnicity, race, weight, height, BMI, Primary Cause of ESRD, Time Since the Start Date for Renal Replacement Therapy (First Ever)/ESRD First Transplant or First Dialysis Ever, Time since the Start Date for Hemodialysis (Most Recent)) obtained before the first study drug administration will be summarized using descriptive statistics by treatment group and all patients for ITT population, Safety Population.

Additional summaries will be provided for each substudy if there are adequate number of patients enrolled.

Age for each patient is defined as number of years between informed consent date and birth date.

For summarizing race, if multiple races are recorded in the database, then 'Multiple Race' is used in the summary table.

The study sample sizes will be summarized by trial unit (site) for enrolled patients. All patients with signed inform consent will be included in the enrolled patients.

Dialysis prescription characteristics (Days of the week dialysis is scheduled, prescribed number of sessions, prescribed duration, dry weight total, type of dialyzer to be used, type of vascular access, Location of Arteriovenous Fistula/Graft and Location of Catheter) will be summarized for ITT population, Safety Population. Additional summaries will be provided for each substudy population if there are adequate number of patients enrolled.

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT). In addition, the frequency and percentage of patients with CHAOS score (0, 1, 2, ... , 6) will be provided for AF substudy population. The CHADS score is the total of the scores per the risk criteria below with data collected from Targeted Medical History CRF.

Score	CHADS2 Risk Criteria
1 point	Congestive heart failure
1 point	Hypertension
1 point	Age 75 years
1 point	Diabetes mellitus
2 points	Stroke/transient ischemic attack

Patient randomization and disposition will be summarized by treatment group and all patients. All patients enrolled will be included in the summary. The summaries will include: the total number of patients were screened, randomized, dosed and included in each population, the number of patients completed treatment, the primary reason for terminating treatment, the number of patients completed post-treatment evaluation period, and the primary reason for terminating post-treatment evaluation period.

In addition, the disposition will be summarized by treatment group and all patients for AF substudy population, PK substudy population, and Platelets Function/Activation substudy population.

All protocol deviations will be listed. Protocol deviations will also be summarized by region, trial unit, and treatment group.

2.3 Safety Analyses

Safety analyses will be based on the safety population. Safety summary tables will be presented by treatment group and ISIS 416858 total.

2.3.1 Exposure

Treatment duration, time on study, number of doses and amount and total volume of Study Drug (ISIS 416858 or placebo) received will be summarized by treatment group and ISIS 416858 total.

The treatment duration (days) for each patient is defined as last dose date - first dose date +1.

The time on study will be defined as the total number of days a patient is known to be followed on study calculated as follows:

Time on study = Last date on study - Date of first dose+ 1.

Where the last date on study is defined as the date of the latest visit with evaluation, or time of death from all available data for a given patient. Visits with refused or unable to contact are not visits with evaluation.

The amount of Study Drug received (mg) for each patient is defined as the total volume (mL) administered from the 200 mg/mL stock solution.

2.3.2 Complia11ce

Percentage of compliance will be calculated and summarized by treatment groups and ISIS 416858 total.

Study drug compliance = 100 x (Total number of doses with injections given I Total number of doses with injections expected).

If a patient discontinued the study treatment, the total number of doses with injections expected is counted, per the schedule of injections, up to the last attended study visit during the treatment period.

2.3.3 Adverse Events

The treatment emergent adverse events (TEAE) are defined as those AEs that occurred after dosing and those existing pre-dose AEs that worsened post-dose during the study.

The most conservative approach will be used to detennine if the event occurs during the treatment or follow-up periods:

- AEs that have onset dates or resolution dates prior to the first study treatment dates will be considered to have occurred prior to the study period. If the onset or resolution date

of an AE is a partial date with only month or year available or complete missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

- AEs that have onset dates after study termination date for the post-treatment evaluation period will be assumed to have occurred after the study period. If the onset of an AE is a partial date with only month or year available or complete missing, then similar approach as above will be used

The ESRD related adverse event is defined as TEAE with "Related", "Possible" relationship to ESRD. If the AE relationship to ESRD is missing or it has been defined as "Unlikely/remote", it will be considered as a Non-ESRD/Procedure-related AE.

All adverse event summaries will be restricted to treatment-emergent adverse events (TEAE).

The incidence of treatment-emergent adverse events will be summarized by treatment group and ISIS 416858 total, by MedDRA preferred term and system organ class for the followings:

- AE Overview
- AE Overview for ESRD/Procedure-related adverse events
- AE Overview for non-ESRD/Procedure-related adverse events
- TEAEs
- TEAE for ESRD/Procedure-related adverse events
- TEAE for non-ESRD/Procedure-related adverse events
- TEAEs potentially related to study drug. Potentially related is defined as "Related", "Possible", or missing relationship to study drug
- Serious TEAEs
- Serious TEAEs potentially related to study drug
- TEAEs resulting in permanently discontinuation of study drug
- Subjects with non-serious AE. The subjects with non-serious AE are those subjects having at least one non-serious adverse event, but no SAE.
- TEAE by maximum severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported one or more events. Adverse events with missing severity will categorized as "Missing" for this summary. Event counts will also be provided for each level of severity.
- TEAEs potentially related to study drug by maximum severity

- Serious TEAEs potentially related to study drug by maximum severity

Events will be sorted by total incidence of each System Organ Class then by total incidence of each Preferred Term within each System Organ Class. For incidence counts, each patient will be counted only once within each Preferred Term and within each SOC. Percentages will be based on the nwnber of patients in a particular treatment ann.

2.3.3 .J Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRJS) is defined as (A) moderate or severe Injection Site Erythema, Swelling, Pruritus, Pain or Tenderness that started on the day of injection, persisted for at least two days; or (B) any AE at the Study Drug injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the Study Drug injection site is the principal reason for discontinuation.

LCRIS will be summarized using the MedDRA coding system, by preferred term. Patients with moderate, severe and any LCRIS will also be swnmarized. Discontinuations due to AE at the injection site will be summarized separately.

Percentage of injections leading to LCRIS will be summarized by preferred terms and overall using the descriptive statistics. Additionally, percentage of Study Drug injections leading to LCRIS will be summarized by the moderate, severe severity and overall discontinuation of study drug due to AE at Study Drug injection site.

Percentage of Study Drug injections leading to LCRIS will be calculated as follows for each subject: (A/B)*l00, where A=number of Study Drug injections with a LCRIS, and B=total number of Study Drug injections. Doses that are split across multiple Study Drug injections are counted as a single injection.

2.3.3.2 Flu-like Reactio11s

Flu-like reactions (FLRs) will also be summarized using the MedDRA coding system, by preferred term.

Flu-like reactions are defined as either (A) flu-like illness or (B) Pyrexia or feeling hot or body temperature increased, plus at least two of the following: Chills, Myalgia, and Arthralgia, starting on day of injection or the next day.

Percentage of injections leading to flu-like reactions will be sun1marized using the descriptive statistics.

Percentage of the injections leading to flu-like reactions will be calculated as follows for each subject: (A/B)*100, where A=number of injections leading to flu-like reactions, and B=total number of injections.

2.3.3.3 Bleedi11g

Major bleeding (MB) is defined as one of the following:

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardia!, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of units of packed red blood cells or whole blood or a fall in hemoglobin of20 g/L(1.24 mmol/L) or more within 24 hours

Clinically relevant non-major bleeding (CRNMB) is defined as overt bleeding not meeting the criteria for major bleeding but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient.

Minor bleeding:

All other acute clinically ove11 bleeding events not meeting the criteria for either major or clinically relevant non-major bleeding will be classified as minor. Minor bleeding will be further categorized as injection site and non-injection site bleeding events.

The incidence of any bleeding event after first dose of study drug will be summarized by treatment group for the Safety Population for all bleeding events except minor bleeding at the injection site. Minor bleeding at the injection site will be summarized separately. The summary will include the following outcomes:

- MB
- CRNMB
- Minor bleeding (Non-injection site and injection site events)
- Combination of MB and CRNMB (with either MB or CRNMB)

The cumulative rate of first major bleeding events after first dose of study drug will be displayed using Kaplan-Meier curves for the safety population. Patients without major bleeding event will be censored at the last visit date with evaluation. Additional information on the Bleeding CRF will also be summarized and/or listed.

2.3.3.4 AE of Interests

Adverse events of interest additionally include the following categories from CRFs:

- Cerebrovascular Accident/Transient Ischemic Attack
- Coronary Ischemia
- Venous Thromboembolism

AE listing will be provided for each AESI category including the seriousness of the AE.

2.3.4 Laboratory Measurements

The following is the list ofroutine lab analytes that may be collected throughout the study:

- Chemistry: Total protein, Albumin, Glucose, Blood urea nitrogen (BUN) for urea reduction ratio (URR) determination, Total bilirubin, Direct bilirubin, Indirect bilirubin, ALT, AST, GGT
- Hematology: Red blood cells, Hemoglobin, Hematocrit, MCV, MCH, MCHC, Platelets, Mean Platelet Volume, WBC, and WBC differential (percentage and absolute) (Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils)
- Inflammatory Markers: Hs-CRP, D-climer, Beta-2-M, Cardiac troponin I and T, NT-proBNP
- Screening Tests: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, FSH (women only, if applicable) and Serum PhCG (women only). This data will only be displayed in patient listings.

Missing WBC differential absolute counts and percentages will be derived as needed:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophils counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Chemistry and hematology panel results, change and percent change from baseline will be summarized by treatment group and study visit.

For ALT and AST, the number and percent of patients falling in each of the following categories for central laboratory data will be tabulated by treatment group:

- Confirmed ALT>= 3x ULN
- Confirmed ALT>= 5x ULN
- Confirmed AST>= 3x ULN
- Confirmed AST>= 5x ULN

A confirmed laboratory value is based on consecutive lab values within 7 days. If that value is in the same or worse category, then the initial value is confirmed. If the consecutive value is in a better category, then the initial value is confirmed using consecutive value category. If there is no retest within 7 days, the initial value is presumed confirmed. If there are multiple results on the same day (no matter from the same lab vendor or different lab vendors), then the worst value will be utilized in the analysis.

BCH flow cytometry data for platelet function will be summarized separately. The Versiti (Blood Centers of Wisconsin) data will be listed.

All patients meeting safety monitoring and stopping rules will be listed.

2.3.5 Vital Signs

Vital signs will include heart rate, respiratory rate, body temperature, and systolic and diastolic blood pressure. For continuous parameters scheduled to be measured in duplicate or triplicate, the mean will be presented in tables and figures.

Summary tables will be created to present the descriptive statistics for vital sign values as well as the change and percent change from baseline at each study visit.

2.3.6 Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as adverse events. All physical examination data will be provided in a data listing.

2.3.7 12-Lead Electrocardiograms (ECG)

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTC (recorded from ECG machine).

Summary tables will be created to present the descriptive statistics for ECG parameters as well as the change and percent change from baseline at each study visits. For continuous parameters scheduled to be measured in duplicate or triplicate, the mean will be used for tables and figures.

For the categorical responses to overall interpretation, counts and percentages will be provided. If multiple results are available, the worst case result will be used in the summary.

2.3.8 Co1tcomita11t Medications

Concomitant medications will be coded using WHO Drug dictionary Version Mar 2018 and summarized by ATC class, generic name and treatment group. Prior medications and Concomitant medications will be summarized by treatment group for the Safety population. Prior medications include medications started and stopped prior to study drug administration (Day 1). Concomitant medications include medications (1) started prior to, and continued after Day l, or (2) medications started on or after Day 1.

All transfusions will be summarized and listed for all patients as recorded on the transfusion logCRF.

2.3.9 Ancillary procedures

Ancillary procedures will be provided in the listing.

2.3.10 Changes in Dialysis Access

Changes in dialysis access prescription will be listed.

2.4 Pharmacodynamic Analyses

The pharmacodynamic analysis will be conducted on the Per Protocol Population and will be presented according to treatment group and ISIS 416858 total. The baseline is defined as the latest- assessment prior to first dose of study drug.

Change and percent change from baseline FXI activity and antigen levels and aPTT will be summarized by treatment and visit separately. Individual results will be presented in data listings by treatment. Figures of the mean FXI activity and antigen levels and aPTT results as well as change and percent change from baseline will be provided by treatment group, and scheduled visit.

Change and percent change from baseline in FXl activity and antigen levels and aPTT will be compared between each of the ISJS-416858 treated group and pooled placebo group using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be tested by applying Kolmogorov-Smimov test on the residuals (difference between individual values and group mean). Numeric values will be rounded to *5* decimal places when applying Wilcoxon Rank Sum test or Kolmogorov-Smirnov test.

Frequency and percent of patients with average FXI activity .1, -2, s>.3, ..., :9.0U/mL during Day 50 to Day 176 (inclusive) up to last dose+ 7 days will also be provided.

The incidence and events for any aPTT>160s will be summarized by treatment and visit.

The clotting assessment will be conducted on the Per Protocol Population and will be presented according to treatment group and ISIS 416858 total.

The clotting assessment will consist of a quantitative scale by descriptive category (see details in table 1) and will be performed by trained personnel.

Table 1 Clotting Scale

Inspection site	Category 1	Category 2	Category 3	Category4
Air Trap	No clotting	Fibrinous ring with no clot formation on venous chamber filter	Clot formation on venous chamber	Coagulated system (treatment cannot continue without new setup)
Dialyzer	Clean dialyzer	Blood stripes affecting less than 5% of the fibers seen al the surface of the dialyzer	Blood stripes affecting 5% or more of the fibers seen at the surface of the dialyzer	Coagulated filter

Overall score Is the highest of the Individual component scores

Individual Category Summary

The frequency and percentage of patients in each clotting category will be summarized by inspection site (air trap, dialyzer) for each visit including screening visit. The overall score for individual clotting category, which is the highest of the inspection site Air Trap and Dialyzer score, will also be summarized.

In addition, the frequency and percentage of patients for overall score in each clotting category will be summarized by the following visits:

Week 26 or ET results for patients completed Week 8.

The denominator is the number of patients with at least one non-missing clotting assessment for each specific period above. The overall score for individual clotting category (1, 2, 3, or 4) will be analyzed for treatment comparison between each of the ISIS-416858Treated group and placebo group using the Wilcoxon Rank Sum test.

Tn addition, the overall score for individual clotting category (1, 2, 3, or 4) will be analyzed using the proportional odds model with treatment as main effect. The proportional odds model with treatment as main effect and baseline clotting category as covariate will also be provided. P-value, odds ratio, and 95% confidence interval will be provided.

At least one clotting category >= 3

The frequency and percentage of patients with at least one post-baseline clotting category 3 or greater event after Week 8 (Day 50) and up to last dose+ 7 days will be summarized by treatment group for each of the following periods for subjects on treatment:

- Before Week 8
- After Week 8 and up to last dose + 7 days

The denominator is the number of patients with at least one non-missing clotting assessment after Week 8 and up to last dose+ 7 days. The corresponding Ex.act Binomial 95% confidence interval will be provided.

A logistic regression model with treatment as main effect will be used to test the treatment difference between ISIS 416858 versus placebo in the proportion of patients with at least one clotting category 3 or greater. An estimate of the odds ratio, p-value and two-sided 95% confidence interval will be computed from the model using Wald's test. The logistic regression model with treatment as main effect and baseline clotting category as covariate will also be provided.

In addition, the number of events across all subjects of dialysis circuit will be summarized by treatment group.

Patient percentage of events greater or equal to 3 will be summarized for 2 periods (before Week 8, after Week 8 and up to last dose+ 7 days). The change of the percentages will be summarized and analyzed by ANOVA.

Most severe clotting category

In order to examine the correlation of FXI activity level and clotting, a separate summary on the most severe clotting category will be provided for patients with average Pre-dialysis FXI activity :::{).1, :::{).2, :::{).3, ... , :::1.0 U/mL during Week 8 and Week 26 (Day 176) (inclusive) for ISIS 416858 treated patients only.

Additional summary for frequency and percent of events with >=3 clotting category with average Pre-dialysis FXI activity ::0.1, :::{).2, :::{).3, ... , :::1.0 U/mL during Week 8 and Week 26 (Day 176) (inclusive) will also be provided.

2.5 Exploratory Outcomes

The incidence of myocardial infarction **(MI),** stroke, systemic embolism, and cardiovascular (CV) mortality will be summarized by treatment group. In addition, information from the specific CRFs will be summarized for each treatment group.

2.6 Other Study Outcomes and Evaluations

Blood Urea Nitrogen (BUN) will be used for Urea Reduction Ratio (URR) analysis in the Safety population.

$$\mathbf{URR} = (\text{Upre} - \text{Upost})/\text{Upre}) \times \mathbf{100\%}$$

where Upre is the pre-dialysis blood urea nitrogen (BUN) level in serum and Upos1 is the post-dialysis blood urea nitrogen (BUN) level in serum. The URR generated from Lab will be used.

URR and sp Kt/v values as well as the change and percent change from baseline will be summarized for each visit by treatment group for the safety population. Single pool dialyzer clearance of urea (sp Kt/v) from CRF will be used in the summary.

Change and percent change from baseline will be compared between each of the ISIS 416858-treated groups and the pooled placebo group using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be tested by applying Kolmogorov-Smirnov test on the residuals (difference between individual values and group mean).

Changes in dialysis prescription will be listed.

2.6.J Platelet Function tests

All Flow cytometry and PFA results will be summarized by visit and treatment for Platelet Function/Activation Substudy population.

Flow cytometry results (and potentially a report with interpretation of the results) will be provided directly by Boston Children's hospital. Flow cytometry results of platelet-monocyte and platelet-neutrophil aggregates and platelet surface P-selectin and platelet surface activated GPIIb-Illa will be compared between each of the ISIS 416858-treated groups and the pooled placebo group.

The PFA results of duplicate closure times for each evaluated cartridges of collagen/EPI, collagen/ADP, and INNOVANCE PFA®P2Y (optional cartridge) for change and percent change from baseline will be compared between each of the ISIS 416858-treated groups and the pooled placebo group for subjects that have the PFA tests performed.

2.7 Pharmacokinetic Analysis

For pharmacokinetic (PK) assessment, plasma trough PK samples during the 26-week treatment period and post-treatment samples during the 12-week post-treatment follow up period will be collected from all patients in the study. Additionally, extensive plasma PK samples will be collected in the PK subgroup following the first (Day 1) and last (Day 176) SC administration.

PK analysis will be conducted for the PK Population only.

2.7.1 Plasma Concentration Data

Plasma concentrations of ISIS 416858 over time, along with the scheduled (nominal) and actual sampling times (i.e., time from SC dosing) will be listed (when applicable) for each

subject, by group/subgroup, cohort, treatment, and nominal dose. In addition, percent differences between scheduled and actual sampling times, and between nominal dose and actual dose received will also be listed for all patients.

For all patients who receive ISIS 416858 treatment, ISIS 416858 plasma trough and post-treatment concentrations will be summarized using descriptive statistics by cohort, nominal dose, study day, and scheduled time point, without and/or with stratification by subject IM status (see Section 3.8). ISIS 416858 plasma concentrations from the PK subgroup will also be similarly summarized. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as "NA" (not applicable). At the discretion of the PK scientist and/or biostatistician,samples may be excluded from descriptive statistics ifthere are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose (e.g., percent difference between scheduled and actual sampling times, or between nominal and actual dose greater than 30%). Any samples excluded from the summary descriptive statistics, if deemed necessary, will be listed separately along with the reason for exclusion.

For all evaluable patients, ISIS 416858 plasma trough (predose) and post-treatment concentrations versus time (actual) profiles for each individual patient, as well as corresponding mean (±SD) plasma concentration versus time (scheduled) profiles will be presented graphically on linear and semilogarithmic scales, without and with stratification by subject immunogenicity status (see Section 3.8). For the PK subgroup, ISIS 416858 plasma concentration versus time (actual) profiles (up to 24 hours post dose and/or full profiles) following the dose on Days 1 and 176, as well as the mean(± SD) plasma concentrations versus time (scheduled) profiles without and/or with stratification by subject IM status, will be presented graphically on linear and semilogarithmic scales. At the discretion of the PK scientist and/or biostatistician, samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose (e.g., percent difference between scheduled and actual sampling times, or between nominal and actual dose greater than 30%).

2.7.2 Plasma Pharmacokinetic Parameters

Noncompartmental PK analysis of ISIS 416858 will be carried out on each individual patient data set where full PK sampling profiles and/or post-treatment profiles are collected using Phoenix WinNonLin Version 8.0 or higher (Pharsight Corp., Mountain View, CA). Plasma pharmacokinetic parameters in each subject (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK

parameters will be calculated (when applicable and not necessarily limited to) and based on actual sampling times:

1. Cmax: the maximum observed ISIS 416858 concentration in plasma will be detennined on Day 1 and Day 176 for patients in the PK subgroup only.
2. Tmax: the time at which Cmax occurs will be determined on Day 1 and Day 176 for the PK subgroup only.
3. AUCo-24hr: partial area under the plasma concentration-time curve (AUC) from time zero to 24 hours will be calculated using the linear-up log-down trapezoidal rule on Day 1 and Day 176 for patients in the PK subgroup only.
4. AUCo-4Shr: partial area under the plasma concentration-time curve (AUC) from time zero to 48 hours will be calculated using the linear-up log-down trapezoidal rule on Day 176 for patients in the PK subgroup only.
5. AUCo.t6Shr (AUCt): partial area under the plasma concentration-time curve (AUC) from time zero to 168 hours wilJ be calculated using the linear-up log-down trapezoidal rule on Day 176 for patients in the PK subgroup only.
6. CLsslF (L/hr): Plasma clearance at steady-state will be calculated from CLsJF = Actual Dose/AUC0.16&hr for dosing on Study Day 176 for patients in the PK subgroup only.
7. Vz/F (L): Apparent volume of distribution in the tenninal phase will be calculated from Vz/F = CLsslF/ AZ for dosing on Study Day 176 for patients in the PK subgroup only.
8. tl/21z: apparent terminal elimination half-life will be calculated from the equation, t1mz= 0.693/Az, where J.z is the rate constant associated with the apparent terminal elimination phase. A minimum of three data points in the elimination phase will be used to define J.vz. and the correlation of determination values (r2) has to be at or greater than 0.8 for the estimate to be accepted. This parameter will only be calculated following the dose on Day 176 for all evaluable patients (including subjects participating in the PK subgroup) receiving active study drug ISIS 416858 (i.e. **PK** set).

Plasma pharmacokinetic parameters (if applicable) will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by cohort, nominal dose, and day (as deemed appropriate).

Plasma pharmacokinetic parameters will be listed by cohort, dose, subject ID, subject IM status, and study day; and appropriately summarized (separately for the PK subgroup and all evaluable ISIS 416858 treated patients) using descriptive statistics (n, mean, SD, SE, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by study day. Additionally, subject IM status stratified (see Section 3.8) plasma pharmacokinetic parameters will be similarly summarized (again separately for the PK Subgroup and all

evaluable ISIS 416858 treated patients). Other stratifications may also be performed if deemed warranted at the discretion of the pha1macokineticist and/or biostatistician.

Exposure-response relationships between selected pharmacodynamic (including but not limited to FXI antigen level and FXI activity) and pharmacokinetic measures (including but not limited to plasma trough concentrations) may also be explored (including with and without stratification by IM status), where appropriate.

2.8 Immunogenicity (IM) Analysis

Samples collected at pre-dialysis/pre-dose on Days 1, 15, 29, 85, 176, and anytime on Day 260, including early termination samples for IM assessment will be analyzed for anti-ISIS 416858 antibodies (ADA). However, plasma samples collected at other time points (for PK purposes) may also be potentially evaluated if deemed of further interest and warranted by the pharmacokinetic scientist. An evaluable sample will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'IM negative'. Sample IM results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS 416858 antibodies) before, during, and after treatment with study drug (ISIS 416858 or placebo) (sample IM status) will be listed by treatment and dose.

Study subjects will be given 'lM positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. Study subjects will be given 'IM negative' status if all evaluated IM sample results during the treatment and post-treatment evaluation periods are IM negative and they have at least one evaluable IM result collected post study drug treatment. Otherwise, a study patient will be given 'unknown' IM status. Subject IM results will be listed by treatment and dose for all evaluable patients, which will include but may not be limited to: subject JM status (positive, negative or unknown), the study day associated with the first positive TM status emerged (T1ii-s1, i.e., onset of ADA development), the last positive IM status observed (T1as1), the time of last evaluable IM sample collected (T1as1 sampling), peak titer, and time to reach peak titer. The onset of ADA and time to reach peak titer will be calculated by:

- Onset in days= The date of first sample has "positive" sample IM status - first dose date +1;
- Time to reach peak titer in days= Thedate of first peak titer observed- first dose date +1;

Other immunogenicity data analysis (e.g. classification as transient or persistent status for IM positive subjects) if there is sufficient number of patients with transient IM status. Transient and Persistent ADA definitions are defined below and based on Shankar et al. (2014).

Transient ADA response will be defined as:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA response will be defined as:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The sample IM incidence (number) and incidence rate (percent) at each evaluated study time point, and for the overall treatment and post-treatment evaluation period, as well as subject IM incidence and incidence rate, will be determined and appropriately summarized by treatment, as the total number of and percentage of evaluated subjects with IM negative, positive, and unknown status. Subjects with positive IM status may further be classified as transient or persistent status if applicable, and incidence and incidence rate for being transient or persistent will be appropriately summarized. Furthermore, onset, titer over time, and peak titer of the ADA response, if applicable, will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range and presented graphically, if deemed appropriate, by treatment at the discretion of the designated study pharmacokineticist and/or statistician (e.g., summarized at each evaluated study time point and overall; summarized by observed peak titer values from the individual IM positive subjects; etc.).

In addition to PK assessments (Section 3.7), selected safety (Section 3.3) and efficacy (Sections 3.4 to 3.5) assessments may be further stratified by subject IM status (i.e., subject IM status being positive, negative or unknown) and presented in tables and/or graphically, as deemed appropriate or warranted by the designated study pharmacokineticist, medical monitor, and/or biostatistician. Other stratifications (e.g., based on antibody titer, onset of ADA, etc.) of selected PK, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pbarmacokineticist, medical monitor, and/or biostatistician.

Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

NCT Number: NCT03358030

Document Date: Protocol Version 2: 14 June 2018

1. STUDY INFORMATION

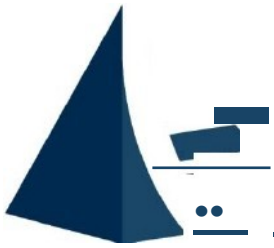
1.1. Protocol and Protocol Amendments

The protocol was amended 1 time. The latest versions of the protocol (Protocol Amendment 1) are provided along with the change summary for the revisions.

Prntocol Version	Date	Document Prnvided
Original	01 June 2017	None
Protocol Amendment 1	14 June 2018	Protocol and change summaiy
Protocol Amendment 1 for Czech Republic	15 June 2018	Protocol and change summaiy
Protocol Amendment 1 for Austria	18 June 2018	Protocol and change summaiy

Notes to File	Date
Pregnancy Test will be Perfmmed Once Every Month for Females of Childbearing Potential in Austria	31 July 2017
Protocol Clarification for Exclusion Crite1ia #2 and Day 2 Schedule of Procedures	18 December 2017
ISIS 416858-CSS - Blinded Safety Data Reviews	21 June 2018
ISIS 416858-CSS Randomization of Subject- with> 28-day Screening Period for Procedures	26 June 2018
Subject Data: Start Time and End Time of Dialysis Sessions	9 July 2018
ISIS 416858-CSS Protocol Clarification for Pregnancy Re-Testing	16 July 2018
ISIS 416858-CSS Protocol Clarification for Continuing on Study when Study Drng is Discontinued	1 August 2018
Dosing Etrnr Subject- (Randomization-) atSite-	3 August 2018
ISIS 416858-CSS Clar·ification for Re-Testing of Subjects that have Platelets < 150,000/mm^3 During Screening	22 August 2018
ISIS 416858-CSS FXI Rainin Pipette Calibration Validation Pe1iods	6 September 2018
ISIS 416858-CSS and Emollment ofMYTEMP Patients in Canada	10 September 2018
Unblinding of Lab Data for ISIS 416858-CSS Patient- (Rand-)	1 September 2018
Clarification of Aspirin and/or NSAID Use in Subjects in the Platelet Substudy	24 September 2018
ISIS 416858-CSS FXI Activity and Antigen Levels	19 October 2018
Immediate Change for Shipment Temperature of Hematology Samples (Sites [redacted])	28 December 2018
ISIS 416858-CSS Unblinded Local Lab Entiy	4 March 2019

Notes to File	Date
Additional Medical Monitoring Requests in Study ISIS 416858-CSS	5 April 2019
ISIS 416858-CSS Per-Protocol Set (PPS)	7 June 2019
ISIS 416858-CSS Disallowed Concomitant Medication and Per-Protocol Set (PPS) Analysis	4 September 2019
ISIS 416858-CSS Study Dmg Intem1ption or Discontinuation Due to Low Platelets	4 September 2019
ISIS 416858-CSS Data Enny Enors: Date of Dosing	8 October 2019



ION IS™ PHARMACEUTICALS

IONIS PHARMACEUTICALS, INC.

ISIS 416858-CSS

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRXan Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Protocol Amendment 1-14 June 2018

EudraCT No: 2017-002165-21

Sponsor:

Ionis Pha1maceuticals, Inc.
2855 Gazelle Comt
Carlsbad, CA 92010

ISIS 416858-CSS

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Protocol Amendment 1-14 June 2018

Protocol History:

Original Protocol: I JWie 2017

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 GazeJJe Court
Carlsbad, CA 92010
[redacted]
[redacted], MD, PhD
[redacted] – CardioMetabolics

ISIS 416858

(BAY 230 6001)

lonis Protocol Number ISIS 416858-CSS

Protocol Amendment 1

EudraCT No: 2017-002165-21

Clinical Phase: 2

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Trial Sponsor:
Ionis Pharmaceuticals, Inc.
2855 Gazelle CoUI1
Cru.-Isbad, CA 92010

Telephone: +1 760-931-9200

Key Sponsor Contact:
[redacted] MD,PhD
2855 Gazelle CoUii
Carlsbad, CA 92010

Telephone: [redacted]
Fax: [redacted]

Date: 14 June 2018

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 416858-CS5
Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pha1macokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXfax an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis
Amendment:	Protocol Amendment 1
Date:	14 June 2018

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Phaimacokinetics, and Phaimacodynamics of Multiple Doses ofISIS 416858 (IONIS-FXfax an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis" dated 14 June 2018, and agree to conduct the study as described herein.

I agree to comply with The International Council for Harmonisation of Technical Requirements for Pha1maceuticals for Human Use (ICH) E6.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Jonis Pha1maceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 416858-CSS

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Phannacokinetics, and Pharmacodynamics of Multiple Doses ofISIS 416858 (IONIS-FXhx an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Amendment Number: I

Amendment Date: 14 June 2018

The prima1y pmpose of this amendment is to fmther clarify ce1tain aspects of the protocol and to simplify procedmes for the study site. Other changes will allow study sites to better prepare subjects for the study and provide added flexibility for study subjects with a longer timeframe for signing of the info1med consent and greater visit windows, respectively.

Minor changes (not included in the list of changes below) have been made throughout the protocol to conect e1rnrs and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summa1y list of major changes to the protocol:

Protocol Section(s)	Description of Change	Rationale
Synopsis Study Design Schema Section 3.4 Section 8.3 Section 8.6 Section 8.7	Clarified that subjects are encouraged to complete the entire treatment and post-treatment evaluation periods, even if Study Drug (ISIS 416858 or placebo) has been discontinued.	In this safety study, it is important to obtain a complete safety set in order to complete an intent to treat analysis. Additional text provides clear expectations for subject and sites.
Exclusion Criteria (Synopsis Section 5.2)	Added to Exclusion Criteria #3 to include FXI activity< 0.3 U/ml atScreening.	Provides clarification on screening laboratory procedures to be evaluated for subject eligibility.
Exclusion Criteria (Synopsis, Section 5.2) Synopsis Section 8.9.1 Concomitant Therapy	For subjects in the optional platelet function substudy, aspirin or NSAIDs use is now allowed.	Removing the disallowed concomitant therapy of aspirin and NSAIDS for the platelet function subgroup will improve recruitment into the substudy with minimal effects expected for study results based on the requirements of the primary platelet function assays selected.

Protocol Section(s)	Description of Change	Rationale
Synopsis Study Schema Section 3.4 Section 4.1 Section 6.1.1 Appendix A	Extended the screening period for signing of the Informed Consent from 28 days to 49 days	Allows study sites to prepare subjects for the study screening procedures in a timely manner at the convenience of the sites and subjects.
Synopsis Section 3.4.1 Section 8.1 Appendix A	Provided additional clarification on the expected completion of dialysis and Study Drug administration.	Provides more details on dialysis completion and when it is appropriate to administer Study Drug.
Synopsis Section 3.1 Section 4.2	Clarified that subjects are also stratified based on their participation in either or both of the substudies (pharmacokinetic and/or platelet substudy) as applicable.	Added language provides necessary details by which stratification is occurring for substudy participants.
Section 2.3.3.2	Added the preclinical toxicology assessments with respect to the proposed dose levels in the study.	Added details of the relative exposures for humans in preclinical toxicology studies.
Section 6.1.3 Section 6.1.4 Appendix A	Added increased window time for visits occurring in the treatment and post-treatment periods.	Reduces subject burden to increase flexibility without affecting subject safety.
Section 9: Serious and Non-Serious Adverse Event Reporting	• Clarified Adverse Event (AE) definition in Section 9.3.1 • Added adverse drug reaction (ADR) in Section 9.3.2 • Added Adverse Event of Interest (AEOI) as Section 9.3.4 • Clarified in Section 9.4.1 that an SAE should be reported electronically whenever possible	Clarifies terms used in the Safety sections of the protocol and required reporting.
Section 9.5.4 Contraception and Pregnancy	Clarification of the expected pregnancy follow-up period was provided.	Clarifies the follow-up for an outcome of pregnancy for subjects.
Appendix A	Clarified that KW assessments will also be recorded on study visits determining URR.	Ensures that 2 measures of dialysis adequacy are evaluated during the study.
Appendix A	Clarified that the 2 additional ECG measures at specified visits are not required. Only 1 ECG measure is required per timepoint for the study.	Reduces subject burden without affecting study results.
Appendix A	Removed the repeat pregnancy testing during screening of women determined to not be of child bearing potential and clarified the testing of women of child-bearing potential.	Reduces subject burden during screening without affecting subject safety and clarifies for site staff the recurrent testing of women of child-bearing potential.

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRXan Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis.
Study Phase	2
Indication	Evaluation of the antithrombotic effects of ISIS 416858 in patients with end-stage renal disease (ESRD) receiving chronic hemodialysis.
Primary Objectives	To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ISIS 416858 (200,250, and 300 mg once-weekly) as compared to placebo.
Exploratory Objectives	Incidence of myocardial infarction **(MI),** stroke, systemic embolism, and cardiovascular (CV) mortality
Study Design	This is a Phase 2, multi-center, stratified, randomized, double-blind, placebo-controlled study of ISIS 416858 (IONIS-FXIRXan Antisense Inhibitor of Factor XI) treatment for up to 26 weeks in ESRD patients receiving hemodialysis at least 3 times a week. Subjects included in this study will maintain all of their standard of care dialysis treatments (including heparins) as determined by their treating practitioners. Subjects will be stratified based on the diagnosis of documented atrial fibrillation at Screening, and then subjects will be randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Additionally, the subjects will also be stratified based on their participation in the substudies (pharmacokinetic and/or platelet substudy) as applicable. Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive subcutaneous treatment with Study Drug (either ISIS 416858 or placebo). Cohorts A, B, and C Patients in Cohort A will be randomized to receive once-weekly either 200 mg ISIS 416858 or placebo, subjects in Cohort B will be randomized to receive either 250 mg ISIS 416858 or placebo, and Cohort C will be randomized to receive either 300 mg ISIS 416858 or placebo. The study will include a 4-week screening period for procedures and a 26-week treatment period followed by a 12-week post-treatment evaluation period. Subjects are encouraged to complete the entire treatment and post-treatment evaluation periods, even if Study Drug (ISIS 416858 or placebo) has been discontinued. Upon completion of screening evaluations, including SC tolerability assessments with 0.9% sterile saline injections, eligible subjects will receive Study Drug weekly for the 26-week treatment period. All doses of Study Drug will be administered subcutaneously (SC) after completion of the hemodialysis treatment, Study Drug can be administered immediately after dialysis is completed when blood is returning to the subject but must be within 2 hours (preferably within 15 minutes of the conclusion of dialysis).
Number of Subjects	Approximately 204 patients are planned to be enrolled in parallel in this study and randomized equally across Cohorts A, B, and C.

PROTOCOL SYNOPSIS *Continued*

Study Population	**Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements. 2. Males or females aged 18 to 85 years old at the time of informed consent. a. Females: must be non-pregnant and non-lactating and either: i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); ii. post-menopausal (defined as 12 months of spontaneous amenorrhea in females> 55 years of age or, in females :S 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved); or, iii. if engaged in sexual relations and of child-bearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug (ISIS 416858 or placebo). b Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug (ISIS 416858 or placebo). 3. End stage renal disease maintained on outpatient hemodialysis at a healthcare center for> 3 months from screening with hemodialysis at least 3-times per week for a minimum of 9 hours per week of prescribed treatment time and plan to continue this throughout the study. **Exclusion Criteria** 1. Subjects with a history of a major medical event (e.g., previous acute coronary syndrome, stroke or transient ischemic attack, or systemic thromboembolic event) within 3 months of screening, major surgery within 3 months of screening, or new major physical examination finding (not accounted for by past medical history), except for documented atrial fibrillation. 2. Active bleeding (as judged clinically-significant by the Investigator) within the past 3 months from screening or documented bleeding diathesis (excluding uremia), coagulopathy, or recent history of prolonged compression time at arteriovenous fistula. 3. Screening laboratory results as follows: Platelet count< 150,000 cells/mm^3 o < 180,000 cells/mm3 for platelet function/activation subgroup **INR** > 1.4 aPTT > upper limit of normal (ULN) FXI activity< 0.3 U/ml ALT or AST > 2 x ULN Total bilirubin > ULN

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Exclusion Criteria** ***Continued***

4. Subject is not willing to have weekly subcutaneous injections over the study period as assessed during screening.
5. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 (first dose) or IV antibiotic use at the time of Screening.
6. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
7. Known history of or positive test at Screening for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B.
8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor (or designee).
9. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer.
10. Any history of previous treatment with an oligonucleotide (including siRNA). Subjects that have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration ;;: 4 months has elapsed since dosing.
11. Attending nephrologist answers "no" to the question, 'Would you be surprised if this patient died in the next year?"
12. Within 6 months prior to screening, have any of the following:
    - More than 3 episodes of severe hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
    - One (1) event of hypoglycemia in which the patient required hospitalization
    - Recurrent syncope and recurrent hypotension in the inter-dialytic period requiring intervention
13. Planned major surgery in the next 6 months, including subjects receiving a kidney transplant or subjects that anticipate changing dialysis modality (i.e. hemodialysis to peritoneal dialysis).
14. Recent history of, or current drug or alcohol abuse as detennined by the Investigator.
15. Concomitant use of anticoagulant/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, clopidogrel) that may affect coagulation (except low dose aspirin (:5100 mg/day)) during Treatment and Post-treatment Evaluation Periods is not allowed. Stable doses of heparins during dialysis are permitted.
16. Uncontrolled hypertension as judged by the Investigator. For example, subjects with a pre- or post-dialysis blood pressure (BP) that is > 180 mmHg on at least 3 of the last 5 dialysis treatments.
17. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study.

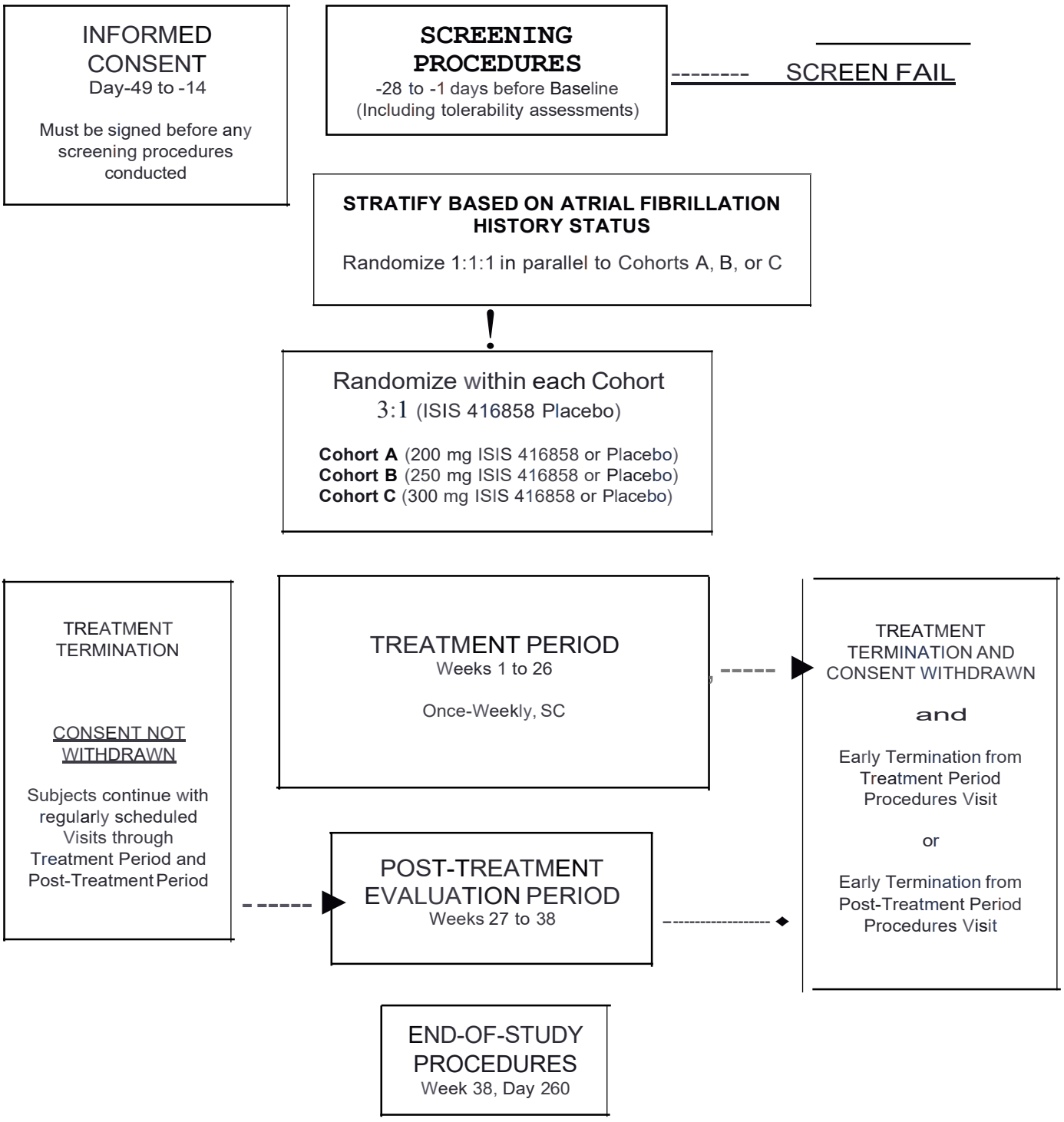
PROTOCOL SYNOPSIS *Continued*

Treatment Groups	There will be 3-dose cohorts that will run concurrently. Subjects will be stratified based on the diagnosis of documented atrial fibrillation and then randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive subcutaneous treatment with either ISIS 416858 or placebo that is added to standard of care hemodialysis therapies as prescribed by their providers, including heparin. Cohort A: Approximately 68 dialysis subjects will be randomized 3:1 to either 200 mg ISIS 416858 or placebo Cohort B: Approximately 68 dialysis subjects will be randomized 3:1 to either 250 mg ISIS 416858 or placebo Cohort C: Approximately 68 dialysis subjects will be randomized 3:1 to either 300 mg ISIS 416858 or placebo
Study Drug Dosage and Administration	The SC Tolerability assessments using 0.9% sterile saline should be administered as two 0.75 ml noncontiguous injections on Study Days S-14 (± 3) and S-7 (± 3). For Cohort A, B and C, the Sponsor will provide ISIS 416858 (200 mg/ml, 1.0 ml) and Placebo (1.0 ml). All doses are given by SC injection. Study Drug will be administered SC post-dialysis at any time from when blood is being returned to the subject but must be within 2 hours (preferably within 15 minutes of dialysis conclusion) for a total of 26 consecutive weeks of treatment in all cohorts. The injection volume will be 1.0 ml for Cohort A (200 mg), 1.25 ml for Cohort B (250 mg) and 1.5 ml for Cohort C (300 mg). Cohorts B and C will be administered Study Drug (ISIS 416858 or placebo) as 2 noncontiguous SC injections.
Rationale for Dose and Schedule Selection	Based on the PK/PD profile of ISIS 416858 in the previous Phase 1 (ISIS 416858-CS1) and Phase 2 (ISIS 416858-CS3 and ISIS 416858-CS4) studies, doses up to 300 mg of ISIS 416858 have demonstrated significant reduction in FXI activity and consequent anti-thrombotic effects without an increased bleeding risk.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in protocol Section 6, and Appendices A and C. The study period for an individual patient consists of signing the informed consent up to 7-weeks (Day -49) prior to randomization, an approximately 4-week screening period for procedures, a 26-week treatment period during which Study Drug (ISIS 416858 or placebo) will be administered SC once-weekly, and a 12-week post-treatment evaluation period. During the screening period, subjects who give written informed consent will undergo a medical history and comprehensive physical examination and have blood samples taken for clinical laboratory testing. Additional tests include a coagulation panel consisting of aPTT, PT/INR, FXI antigen and activity levels. For Screening Days S-14 (± 3 days) and S-7 (± 3 days), subjects shall receive 2 noncontiguous SC injections of 0.75 ml saline to determine tolerability to SC injections. During the treatment period, Study Drug (ISIS 416858 or placebo) will be administered as a SC injection once during Weeks 1 (Day 1), 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, and 26. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, coagulation, immunogenicity, and inflammatory markers), adverse events (including bleeding events), and concomitant medication will be performed according to the schedule of procedures in Appendix A for both treatment and post-treatment evaluation periods. Following the Week 26 visit, subjects will enter the 12-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures ***Continued***	In a subgroup of approximately 12 subjects in each cohort, whose platelet counts are :?: 180,000/mm^3 at Screening, and who are not taking any anticoagulants or antiplatelet agents (other than aspirin), at selected visits during Weeks 1 (pre-dose), 12, 26, and 38, platelet function/activation tests will also be performed (Section 3.1.1, Appendix A). In another subgroup of approximately 12 subjects in each cohort, additional PK sampling will be conducted at their Day 1, Day 2, Week 26 (Day 176, Day 177 and Day 178), and Week 27 (Day 183) visits in order to determine the peak (Cmax), extent of exposure (AUCo-t and AUCo-168), and clearance at steady-state (CLss1F) parameters (Section 3.1.2, Appendix C). Subjects in the platelet function/activation subgroup may also participate in the pharmacokinetic subgroup and may withdraw consent for the subgroup specific procedures (e.g., blood draws for PK) without being withdrawn from dosing or from the study. If a subject withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A. Subjects who discontinue Study Drug are encouraged to remain in the study. Subjects in whom Study Drug treatment should be stopped e.g., when hemodialysis is held for > 2 weeks or stopped, or if there is a change of dialysis modality (i.e., hemodialysis to peritoneal dialysis) including those that receive a renal transplant (See Section 6.2.2) are encouraged to complete the treatment and post-treatment evaluation periods even in the absence of Study Drug administration.
Safety and Tolerability Evaluations	The safety and tolerability of ISIS 416858 will be assessed by determining the incidence and severity of adverse events (including bleeding events) and changes in laboratory evaluations. The primary safety outcome is the combination of major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) during the treatment period (or early study termination). Other safety parameters including (S)AEs, deaths, vital signs, ECG and laboratory parameters will also be recorded. This may include additional information regarding events of interest (i.e. bleeding events, thrombotic events).
Pharmacokinetic Evaluations	Plasma pharmacokinetics will be assessed following the first and last dose in the PK subgroup, whenever possible. Additionally, plasma trough and post-treatment samples will be collected during treatment and post-treatment evaluation period, respectively, for the measurement of ISIS 416858 concentrations.
Pharmacodynamic Evaluations	Coagulation parameters such as FXI activity and antigen, aPTT, PT and INR will be collected and analyzed in a blinded manner throughout the treatment and post-treatment evaluation period visits. The rate/frequency of clotting on the dialysis filters and circuit will be measured as an exploratory analysis.
Statistical Considerations	The sample size was selected based on prior experience to ensure that the safety, tolerability and PK/PD relationships will be adequately assessed while minimizing unnecessary patient exposure. There is no statistical rationale for the selected sample size.
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

2'-MOE	2'-0-(2-methoxyethyl)
ADA	anti-drug antibody
AE	adverse event
AEoI	adverse events of interest
AF	atrial fibrillation
ALT	alanine an1inot:ransferase
aPTT	activated pariial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCo-t	area under the plasma concentration-time curve from time zero to the last observable concentration
AUC0-16shr	area under the plasma concentration-time cmve from time zero to 168 hours
Beta-2-M	beta-2-microglobulin
BP	blood pressure
BUN	blood urea nitrogen
CRNMB	Clinically-Relevant Non-Major Bleeding
CLsJF	apparent systemic (plasma) clearance at steady state after SC administration
Cinax	maximum concentration
CMV	cytomegalovirus
CRO	contract research organization
Dialysis/hemodialysis	process where blood is filtered using a dialyzer and dialysis machine
Dialyzer	ruiificial kidney designed to provide controllable transfer of solutes and water across a semi permeable membrane separating flowing blood and dialysate streams. The transfer processes are diffusion (dialysis) and convection (ultrafiltration)
ECG	electrocru·diogram
eCRF	electronic Case Repori Form
EDC	electronic data capture

ESRD	end-stage renal disease
FFP	fresh frozen plasma
FSH	follicle-stimulating h01mone
FXI	Factor XI
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HAV	hepatitis A virus
Hb	hemoglobin
HBsAg	hepatitis B smface antigen
Hct	hematocrit
HCV	hepatitis C vims
HIV	human immunodeficiency vims
HR	heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international n01malized ratio
IRB	Institutional Review Board
ISIS 416858	antisense inhibitor of Factor XI
IV	intravenous(ly)
IXRS	automated randomization system
kg	kilogram
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mL	milliliter
MPV	mean platelet volume
mRNA	messenger ribonucleic acid
NCS	not clinically-significant

NT-proBNP	N-tenninal pro-brain natriuretic peptide
PD	pha1macodynamic(s)
PK	pharrnacokinetic(s)
PT	prothrombin time
RNase Hl	ribonuclease Hl (a non-specific endonuclease that catalyzes the cleavage of RNA via a hydrolytic mechanism)
SAE	serious adverse event
SAP	Statistical Analysis Plan
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Day 1	defined as the first day Study Drng is administered to the subject
Study Drng	ISIS 416858 or placebo
SUSAR	suspected unexpected serious adverse reaction
Tmax	time to maximal concentration
ULN	upper linlit of normal
VTE	venous thromboembolism
WBC	whlte blood cell
WHO	World Health Organization
W,wk	week
WMA	World Medical Association

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the safety, phaimacokinetics (PK), and phaimacodynamics (PD) of ISIS 416858 (200, 250, and 300 mg once-weekly) as compared to lacebo as assessed b FXI activi ty reduction in ESRD atients on hemodial sis; [redacted]

1.2 Exploratory Objectives

To evaluate the incidence of myocardial infai·ction (MI), stroke, systemic embolism, and cardiovasculai·(CV) m01tality.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

ISIS 416858 is a 2'-methox eth 1 chimeric antisense inhibitor of the molecular tai·get Factor XI (FXI). Preclinical studies suggest that FXI inhibitors can prevent venous and a1terial thrombosis without affecting hemostasis, and congenital FXI-deficient patients have a low incidence of ischemic stroke and venous thromboembolism (VTE) (Schumacher et al. 2010). Thus, selective inhibition ofFXI may represent a novel approach for the prevention of undesired thrombotic events such as VTE and ischemic stroke as well as clotting of hemodialysis circuits which limits the effectiveness of hemodialysis.

2.2 Therapeutic Rationale

Approximately 2 million individuals receive dialysis for end-stage renal disease (ESRD) globally and this number is increasing rapidly as both the incidence of ESRD rises and access to dialysis as a life sustaining therapy increases (Caskey et al. 2011). Dialysis patients are at high risk of thrombotic events due to their high degree of comorbid conditions and because they have a hypercoagulable state. This hypercoagulable state appears to be driven by widely used diugs (e.g., erythropoiesis stimulating agents), inflammation and endothelial dysfunction from uremia, and contact between blood and the extracorporeal circuit. The hypercoagulable state results in clinically meaningful negative outcomes. The risk of stroke in dialysis patients may be 10-times higher than the general population (Sood et al. 2009). Dialysis patients have a 5-fold higher risk of myocai·dial infai·ction than the general population and even moderate chronic kidney disease alone is considered the risk equivalent of diabetes mellitus for cardiovasculai·thrombotic events (Go et al. 2004; Tonelli et al. 2012). Fwthe1more, dialysis patients depend on patent vascular access to receive hemodialysis. Dialysis patients have a high chance, approximately 10% chance per year of having their vasculai· access compromised by thrombosis resulting in a potentially life-threatening situation requiring urgent intervention (Jean-Baptiste et al. 2008; Schild et al. 2008). Finally, dialysis patients ai·e hospitalized an average of 3 times per yeai· and ai·e at high 1isk of VTE (Tveit et al. 2002). Despite this high 1isk ofVTE, there remains considerable unce1tainty as to the benefit-to-risk ratio ofVTE prophylaxis. This is of particulai· importance when considering the optimal treatment for ESRD, renal transplantation, in which VTE can compromise the ability to receive a transplant, the function of an ah·eady transplanted kidney,

and/or the life expectancy of a patient who recently received a transplant (i.e., post-operative VTE) (Irish 2004).

While dialysis patients suffer numerous thrombotic events, they also are at increased risk of bleeding events. ESRD is associated with attenuated platelet aggregation and adhesion, and altered blood rheology. In ESRD patients, blood vessels tend to be compromised from chronic comorbid medical diseases such as diabetes and hypertension, age, repeated phlebotomy and need for vascular access, and chronic exposure to anticoagulants such as hepaiin and antiplatelet agents that are given to maintain vascular access patency and reduce the risk of arterial thrombotic events. Contemporai·y estimates suggest that 1 out of eve1y 7 chronic dialysis patients will be hospitalized for a hem01Thagic event within 3 years of starting dialysis and the risk of major bleeding doubles with the use of anticoagulants (Sood et al. 2014). Patients receiving dialysis are therefore at both high risk of thrombotic events and high risk of bleeding events. This has resulted in a clinical dilemma as the management of dialysis patients at the highest risk for thrombotic events. For example, patients receiving dialysis with concomitant atrial fibrillation are anticoagulated only 37% of the time in North America and only 1% of the time in Germai1y (Wizemann et al. 2010; Tan et al. 2017). Furthermore, the use of vitamin K antagonists in such patients has resulted in a 2-fold increase in the risk of major bleeding and even low-dose anticoagulation (tai·get INR 1.5-1.9) resulted in a 1.5-fold increased risk of major bleeding (Elliott et al. 2007).

In summruy, while the number of patients with chronic renal disease on hemodialysis keeps growing, anticoagulation treatment options to prevent the sequelae ofESRD remain limited. Traditional therapies such as warfruin and aspirin have limited efficacy, perhaps in part due to the mechanisms for thrombosis in ESRD, and expose patients to undue bleeding risk. Therefore, a therapy like ISIS 416858 that is being developed to provide anticoagulation without increased risk of bleeding could effectively reduce thrombosis which may positively affect the morbidity and m011ality in these high-risk patients. Initial data demonstrating that treatment with ISIS 416858 for 12 weeks reduced FXI activity levels up to 80% without any increase in clinically-relevant non-major or major bleeding support this notion. The development of ISIS 416858 will ultimately determine whether the need for hepa1-in during the dialysis procedure could be reduced or eliminated which could reduce the risk of major hemorrhage and improve the dialysis procedure. This concept is supported by a report in the literature of a dialysis patient with severe congenital FXI deficiency (less than 3% of normal) who received hemodialysis for several months without hepru·in or any other anticoagulant and did not exhibit clotting in the extracorporeal circuit or any bleeding complications (Takamizawa et al. 2014). Results from an initial study in 43 ESRD subjects on hemodialysis (ISIS 416858-CS4) indicated that ISIS 416858 significantly reduced the incidence of severe clotting events in the dialyzer circuit at doses of 200 mg and 300 mg per week without increased major or Clinically-Relevant Non-Major Bleeding (CRNMB), providing further supp011 to this finding.

2.3 ISIS 416858

2.3.1 Mechanism of Action

[redacted]

[redacted]

2.3.2 Chemistry

[redacted] These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999); (2) increase resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003); and (3) amelioration of some of the high dose toxicities resulting in an improved safety profile compared to first [redacted]

This is because while the 2'-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2'-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2'-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). [redacted]

2.3.3 Preclinical Experience

Detailed info1mation concerning the preclinical studies conducted with ISIS 416858 can be found in the Investigator's Brochure. A summa1y is included below.

2.3.3.1 Pharmacology

ISIS 416858 and other FXI ASOs have been studied in several species including mice and primates. FXI ASOs have demonstrated antithrombotic activity in FeCb -induced venous and arterial thrombosis mouse models, a stenosis-induced inferior vena cava (IVC) thrombosis mouse model, and a baboon thrombosis model as well as anticoagulant activity in normal mice and monkeys. In all species, FXI ASOs produced 80% reduction of liver FXI mRNA expression and plasma FXI activity as well as prolonged activated partial thromboplastin time (aPTT) (up to 2-fold) in expe1iments ranging from 3 weeks to 12 weeks of treatment without causing spontaneous bleeding or increasing surgically induced bleeding.

2.3.3.2 Pharmacokinetics and Toxicology

Nonclinical PK and toxicology studies oflSIS 416858 in mice and monkeys, conducted in accordance with Good Laborato1y Practices (GLP) standards, have been perfo1med for up to 26 and 39 weeks of treatment in mice and monkeys, respectively. In preclinical studies, ISIS 416858 has shown a similar PK profile (given subcutaneously [SC] or intravenously [IV]) in both mice and monkeys in which drng is cleared within hours from plasma and distributed to tissues with the kidneys having the highest concentration followed by the liver. Subsequently, ISIS 416858 is cleared slowly in tissues via nuclease-mediated metabolism with an elimination half-life of approximately 2 to 4 weeks in both mice and monkeys, which suppmts an infrequent clinical dosing regimen.

In preclinical toxicology studies, the primary findings in the 26-week study in mice were similar to those obse1ved in the 13-week study and were related to the uptake and accumulation of the ASO in tissue and proinflammatmy effects of the ASO treatment. There were also minimal to mild decreases in platelet counts in males at all doses and females at 30 mg/kg/wk ISIS 416858, with a statistically significant reduction only seen in females at 60 mg/kg/wk (ranged from 16 to 44% reduction in group mean compared to control), likely con-elated with increased spleen weights in males at 10 mg/kg/wk and females at 30 mg/kg/wk ISIS 416858 (1.3- to 1.5-fold of control).

In monkeys, the prima1y finding at 6 weeks was the presence of basophilic granules in multiple tissues, which is reflective of cellular uptake of oligonucleotide. The effect was dose-dependent and more prominent at doses of 40 mg/kg/wk. For the chronic 39-week treatment study of ISIS 416858 in the monkey the most notewo1thy finding was the severe reduction in platelet counts in 2/16 monkeys in the 10 and 18 mg/kg/wk groups. These types of platelet reductions were not obse1ved in the 13-week study with doses up to 40 mg/kg/wk. Gradual reductions in mean platelet counts (up to 44%) were also obse1ved at doses 6mg/kg/wk at the end of the 39 weeks dosing with group mean platelet counts still approximately 250,000/mm^3. Up to a 24% reduction in mean platelet counts was also seen in the control group. There was no evidence of bleeding or abnmmality in bone manow hematopoietic cell morphology (including megakaryocytes) associated with either moderate or severe platelet reduction. Minimal to mild

sternal bone manow megakaryocytic hyperplasia (increased numbers of megakaryocytes) was observed in a few animals as a likely response to the decreased platelet counts in these animals.

Plasma and tissue PK observed in monkeys for this class of compounds predict the observed plasma (and expected tissue) exposure levels in humans on the basis of mg/kg equivalent doses. The dose range to be examined in the cmTent clinical study of 200 to 300 mg per week is equivalent to approximately 2.8 to 4.3 mg/kg, respectively, for a 70-kg participant. In our previous clinical trial with ESRD participants on hemodialysis (ISIS 416858-CS4), the mean peak (Cmax) and total exposure (AUC0.24hr) in plasma were 12.0 µg/mL and 150 µg*hr/mL, respectively, following single-dose of 300 mg ISIS 416858 administered SC. In non-human primates, exposure levels ranged from near equivalent Cmax and AUC at 300 mg/wk dose to high multiples depending on the dose level administered. Most systemic toxicities including severe thrombocytopenia were observed at doses 2: 10 mg/kg, and the highest observed mean Cmax values were 206 and 173 µg/mL, while mean AUCo-4shr values were 2150 and 2280 µg*hr/mL, onDays 1 and 91, respectively, following 40 mg/kg per week SC dose studied in the 13-week sub-chronic monkey study (Study No. 416858-AS02PK).

2.3.3.3 Bleeding Risk Evaluation

Cynomolgus monkeys were administered ISIS 416858 (4, 8, 12 and 40 mg/kg/wk, SC) for up to 13 weeks with no spontaneous bleeding events. ISIS 416858 produced a dose-dependent reduction in systemic FXI activity and a concomitant increase in aPTT. Plasma FXI activity was reduced by 80% at 4 weeks of treatment (40 mg/kg/wk) that resulted in a 33% prolongation of aPTT by 13 weeks. No effects on prothrombin time (PT) or platelet counts were observed during this time period, confuming that the effects ofISIS 416858 on FXI inhibition were limited to the intrinsic coagulation cascade. Bleeding parameters were assessed at a 20 mg/kg dose ofISIS 416858 as this dose reduced plasma FXI activity by 50% and 70% after 2 and 6 weeks of treatment, respectively. ISIS 416858 did not increase the risk of bleeding when evaluated in models of bleeding under a surgical setting following partial tail amputation and gum and skin laceration, while positive control enoxaparin at a single-dose of2 mg/kg produced a 2- and 3-fold increase in bleeding time and blood volume loss, respectively, following a pa11ial tail amputation. Bleeding time following gum laceration was also increased by 60% following enoxaparin treatment, while there were no changes in skin laceration bleeding time. These studies suggest that even in tissues with relatively high capacity for fibrinolysis (oral mucosa) ISIS 416858 does not cause bleeding. Thus, it is anticipated that reduction ofFXI levels by administration ofISIS 416858 will not increase bleeding risk. Data from the previous study in ESRD subjects (ISIS 416858-CS4) suppm1 this and demonstrated no increase in CRNMB or MB events despite mean FXI activity reduction by up to 80%.

2.3.4 Clinical Experience

Detailed information regarding the clinical studies conducted with ISIS 416858 can be found in the Investigator's Brochure. ISIS 416858 has been evaluated in 4 clinical studies. The design and status of these studies ar·e summar-ized in Table 1.

Table 1 Summary of ISIS 416858 Clinical Studies

Study	Phase	Study Description	ISIS 416858 Dosage (SC)	Total# Subjects	Center(s) / Country	Study Status
CS1	1	Double-blind, randomized, placebo-controlled, dose-escalation	Single-Dose: 4 dose levels of 50, 100, 200, and 300 mg ISIS 416858 Multiple-Dose: 4 dose levels of 50, 100, 200, and 300 mg of ISIS 416858, 8 doses over 6weeks Week 1: 3 doses on Days 1, 3, and 5, Weeks 2 to 6: once-weekly	88	Single/ Canada	Completed
CS2	1	Drug-Drug Interaction study Multiple-dose drug interaction study with enoxaparin	200 mg ISIS 416858, total of 6 injections during 4 weeks of treatment. A single-dose of 40 mg enoxaparin. administered SC alone or in combination with ISIS 416858 on Day 1 and 1 week after the last dose of ISIS 416858	15	Single/ Canada	Completed
CS3	2	A Phase 2, open-label, randomized, active comparator-controlled, adaptive parallel-group dosing, international multiple-center study in subjects undergoing primary unilateral total knee arthroplasty	200 or 300 mg ISIS 416858 once on Days 1, 3, 5, 8, 15, 22, 29, 36 (6 hours post-surgery) and Day 39 (3 days after surgery) Enoxaparin 40 mg administered SC the evening prior to surgery (optional), 6 to 8 hours after surgery followed by daily injections for at least 8 additional days post-surgery	314	3/Bulgaria 2/Canada 3/Latvia 5/Russia 6/Ukraine	Completed
CS4	2	A Phase 2, double-blind, randomized, placebo-controlled study in ESRD subjects receiving a minimum of 3 hours of hemodialysis 3 times a week	PK Cohort: 300 mg, 2 doses on Days 1 and Day 29 Cohort A: 200 mg ISIS 416858 Cohort B: 300 mg ISIS 416858 Cohorts A and B were administered ISIS 416858 on Study Days 1, 5, 8, 12, 15, 22, 29,36,43,50,57,64, 71,and 78	49	8/Canada	Completed

2.4 Rationale for Dose and Schedule of Administration

The cunently proposed 200,250, and 300 mg ISIS 416858 dosing regimens were selected based on results from the previous Phase 1 and Phase 2 clinical studies that showed a satisfactory safety profile and significant PD effect with these regimens. Specifically, significant efficacy was observed in the ISIS 416858-CS3 study at both the 200 mg and 300 mg doses of ISIS 416858, which resulted in FXI activity reductions to 0.38 ± 0.01 and 0.20 ± 0.01 U/mL, respectively. Treatment duration of 12 weeks in ESRD subjects with both 200 mg and 300 mg dose levels ofISIS 416858 demonstrated an acceptable safety and tolerability profile. Therefore,

the treatment duration in the cmTent study has been extended to 26 weeks to evaluate the safety of ISIS 416858 at clinically efficacious levels for an additional 14 weeks at steady-state in a larger number of patients.

At the doses and treatment duration proposed, FXI activity levels are expected to reach maximal reduction of approximately 80%, with absolute FXI activity being reduced to :'.S 0.2 U/mL. The proposed target level of :'.S 0.2 U/mL FXI activity is fmiher supported by the following safety observations: (i) Patients with severe congenital FXI deficiency (FXI activity levels :'.S 0.2 U/mL) have a low repmted incidence ofVTE and do not appear to have an increased bleeding risk (Asakai et al. 1991; Salomon et al. 2006); (ii) Healthy subjects treated with ISIS 416858 (ISIS 416858-CSl) did not exhibit spontaneous bleeding or any other target related safety concern despite reductions in plasma FXI activity of :'.S 0.2 U/mL; (iii) No increase in bleeding has been obse1ved in the Phase 2 studies for ESRD subjects (ISIS 416858-CS4) or patients undergoing knee a1ihroplasty after FXI reduction with ISIS 416858 compared to standard treatment of 40 mg/day of enoxaparin (ISIS 416858-CS3), despite FXI activity levels of :'.S 0.1 U/mL (Buller et al. 2014).

Fmihe1more, based on nonclinical and Phase **1** and Phase 2 clinical data, approximately **4** to 6 weeks of once-weekly dosing is required to achieve a reduction in FXI activity that will result in clinically meaningful anticoagulation activity after ISIS 416858 treatment.

The safety data obtained **in** the Phase 1 study (ISIS 416858-CSl) and Phase 2 studies (ISIS 416858-CS3 and ISIS 416858-CS4), as well as the clinical experience with several other 2'-MOE-modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006), suppo1is the dosing regimen planned for this Phase 2 study. The planned regimen has been employed safely in previous clinical studies with a number of other ASOs. This class of ASOs has been safely administered IV and SC in multiple clinical studies at doses up to 1000 mg (Kwoh 2008) and treatment durations that exceed 24 months.

2.5 Benefit-Risk Assessment

The known potential risks to study participants associated with ISIS 416858 are elaborated on in the Guidance to Investigator section of the Investigator's Brochme. Additional study associated potential safety considerations include thrombocytopenia and increased major or CRNMB, which will be monitored closely.

Thrombocytopenia is a potential safety consideration based on preclinical GLP studies of ISIS 416858 in monkeys in which 4 of 32 monkeys in the> 10 mg/kg/wk dose groups developed severe thrombocytopenia (< 50,000/mm^3). Grade 4 (< 25,000/mm^3) thrombocytopenia has also been observed clinically with 2 other second generation ASOs in 2 different rare disease populations within the same chemical class as ISIS 416858 at doses> 200 mg/wk. If platelet count is :'.S 100,000/mm^3, then weekly monitoring will be implemented (see Section 8.5.2). In the event of a platelet count< 75,000/mm^3, additional laboratory investigations will be conducted (see Section 8.5.2). Short-term steroid use will be recommended if platelet count< 50,000/mm^3. This is based on data from other programs at lonis demonstrating that sho1i-te1m steroid use improves recove1y from thrombocytopenia. Additionally, no dose of Study Dmg will be administered before reviewing a valid platelet result. Valid platelet counts must be conducted eve1y 2 weeks and reviewed prior to dosing. If the platelet result is unavailable (e.g., due to

hemolysis, clumping, etc.) from the central lab, a repeat local lab will be conducted and reviewed prior to dosing.

fucreased major or CRNMB is also a potential safety consideration given the antithrombosis effects ofISIS 416858 investigated in this study. Clinical findings in Hemophilia C patients have demonstrated increased bleeding in the complete absence of FXI activity (seen mostly in high fibrinolytic tissues and at absolute FXI concentrations< 0.3 U/mL). However, increased major or CRNMB has not been obse1ved to date with ISIS 416858 in the clinic or in preclinical studies. If bleeding were to occur, it can be rapidly reversed with infusion of plasma-derived FXI concentrate (Zhang et al. 2010) as well as specific FXI antidote (where available). Specific instrnctions for its use will be provided to site staff.

Based on the experience from previous clinical studies, it is anticipated that study subjects may benefit (anticoagulation) during the study although long te1m benefit cannot be assessed due to relatively sholi duration of the study.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2 multicenter, double-blind, randomized, stratified, placebo-controlled study in ESRD subjects receiving hemodialysis at least 3 times per week for a minimum of9 hours per week. Subjects will be stratified based on the diagnosis of documented atrial fibrillation (AF) at Screening (Yes/No), and then subjects will be randomized to **1** of 3 dose coholis in a 1:1:1 ratio (Coholi A, Cohmt B, and Cohmi C). Additionally, subjects will be stratified by pa1ticipation in the substudies. Within each dose cohmi, subjects will be randomized in a 3:1 ratio to receive SC treatment with either ISIS 416858 or placebo (See Study Design and Treatment Schema). All standard of care hemodialysis therapies as prescribed by their providers, including heparins, will be continued.

CoholiA: 200 mg ISIS 416858 or placebo SC (3:1)

Coho1t B: 250 mg ISIS 416858 or placebo SC (3:1)

Coholi C: 300 mg ISIS 416858 or placebo SC (3:1)

All cohmts will consist of up to 4-week screening period for procedures and a 26-week treatment period followed by a 12-week post-treatment evaluation period.

The SC Tolerability assessments using 0.9% sterile saline should be administered as 2 noncontiguous injections during the screening period on Study Days S-14 (± 3) and S-7 (± 3). Emolled subjects will receive a SC dose of Study Drng (200 mg, 250 mg, or 300 mg ISIS 416858, or placebo) approximately weekly from Week **1** (Day 1) through Week 26.

The windows for study visits are specified in the Schedule of Procedures (Appendix A); please note that the Study Drng (ISIS 416858 or placebo) dose may not be administered more than once on the same day. Any questions on study procedures and visit windows may be directed to the Sponsor (or designee).

3.1.1 Platelet Function/Activation Subgroup

fu a subgroup of approximately 12 subjects in each coho1t, platelet function and/or activation will be assessed. These subjects must have platelet counts that are 180,000/mm^3 at Screening and who are not taking any anticoagulants or antiplatelet agents (other than aspirin).

At regularly scheduled visits during Weeks 1 (pre-dose), 12, 26, and 38, additional blood samples will be collected and processed for platelet function and/or activation tests as shown in Appendix A.

3.1.2 Pharmacokinetic Subgroup

fu a subgroup of approximately 12 subjects in each coho1t, additional Oto 24-hour PK sampling will be conducted following the first (Day 1, Week 1) and last dose (Day 176, Week 26) in order to dete1mine the plasma PK parameters ofISIS 416858 in ESRD subjects, e.g., peak maximum concentration (Cmax) and total plasma exposure (AUCo-t and AUC0-16shr), as well as clearance at steady-state (CLsslF). Subjects in this subgroup will have additional visits to the clinic to collect blood after dosing on Day 1, including a 24-hour (Day 2), and post-dose blood draw after Day 176 dose (Week 26) at 24-hours (Day 177), 48-hour (Day 178), and 7 days (Day 183). fu the event that dialysis is perfo1med on these days, the blood draw should occur pre-dialysis. For more details of PK sampling schedule, see Appendix C.

Subjects in the platelet function/activation subgroup may also pa1ticipate in the PK subgroup and may withdraw consent for the subgroup specific procedures (e.g., blood draws for PK) without being withdrawn from dosing or from the study. If a subject withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Subjects

Approximately 204 subjects are planned to be enrolled in parallel in this study and randomized equally across Coho1ts A, B, and C.

The 3 multiple-dose cohol1s are designed to assess the safety, tolerability, PK/PD of ISIS 416858. The sample size has been selected to ensure that the PK/PD, safety, and tolerability ofISIS 416858 will be adequately assessed while minimizing unnecessary subject exposure.

3.4 Overall Study Duration and Follow-up

For all coho1ts, the Study will consist of a 4-week screening pe1iod for procedures after the inf01med consent is signed. An additional 21 days is pe1mitted p1ior to screening period for signing of the inf01med consent. All cohol1s will consist of a 26-week Treatment Period, and a 12-week Post-Treatment Evaluation Period. For all coho11s, please refer to the Schedule of Procedures in Appendix A.

Subjects may be required to attend additional visits for monitoring of adverse events (AE) or abnormal investigation results. The frequency of additional monitoring will be determined by the Investigator in consultation with the Sponsor.

If Study Drug is discontinued for any reason, subjects are encouraged to continue their regular assessments for the duration of the treatment period and post-treatment evaluation period, unless subject informed consent is withdrawn.

3.4.1 Screening

After signing the infmmed consent fmm, subject eligibility for the study will be dete1mined within 4 weeks prior to Study Day 1.

During the screening period, at Study Days S-14 (± 3) and S-7 (± 3), subjects should receive 2 noncontiguous SC injections of 0.75 mL saline. As with Study Drug, these may be administered immediately after dialysis is completed when blood is returning to the subject but must be within 2 hours after dialysis (within 15 minutes is prefen-ed) to determine tolerability to SC injections.

All women will have a serum pregnancy test done between Study Days S-28 and S-14 that must be resulted prior to dosing on Study Day 1.

All screening lab re-tests should be resulted by the central lab prior to randomization on Study Day 1.

3.4.2 Treatment

Eligible subjects will receive study treatment every week for 26 weeks. The treatment period consists of the period from the first Study Drug (ISIS 416858 or placebo) injection to the last injection on Day 176 (Week 26), or early study termination.

3.4.3 Post-Treatment

Subjects will have follow-up evaluation visits on Study Week 27 (PK Subgroup only), and for Shrdy Weeks 28, 30, 32, 34, 36, 38 (all subjects), or early study termination. The final study visit will be Study Day 260.

3.5 End-of-Study

The End-of-Study is defined when the la.st subject has had their la.st visit.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the Study, the Sponsor or designated contract research organization (CRO) requires a copy of the Study Center's written institutional review board (IRB) approval of the protocol, informed consent form, and all other patient information and/or recruitment material.

Subjects must sign the consent fmm before any screening tests or assessments are performed, this can be done up to 49 days prior to randomization. At the time of consent, the patient will be

considered enrolled into the Study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed.

Screening labs must be perf01med within 28 days before Study Day 1. If screening labs are to be perf01med outside of this window, then additional samples should normally be drawn prior to Study Day 1 to ensure that labs still fulfill the eligibility criteria. A single re-test of abn01mal screening labs may be done at the central lab to evaluate subject eligibility.

During the screening period, at Study Day S-14 (±3) and S-7 (±3), subjects should receive 2 noncontiguous SC injections of0.75 mL saline as described in Section 3.4.1.

At the time of randomization, subjects will be assigned a unique subject identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to that subject. The screening number and subject identification number must remain constant throughout the entire trial. In the event the subject is re-consented and re-screened, the subject must be given a new screening number. Screening numbers and subject identification numbers, once assigned, will not be re-used.

4.2 Randomization

Subjects will be randomized on Study Day 1 after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

All subjects will be randomized using an automated system (IXRS). Subjects will be stratified based on the diagnosis of documented AF at Screening (Yes/No). Additionally, subjects will be stratified by paiiicipation in the substudies. Then, subjects will be randomized in parallel to 1 of 3 dose cohorts in a 1:1:1 ratio (Coh01i A, Coh01t B, and Coh01t C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive SC treatment with either ISIS 416858 or placebo.

4.3 Unblinding of Treatment Assignment

The Sponsor and all subjects, monitors, and Study Center personnel related to the Study, will be blinded throughout the Study. However, if a subject has suffered a Serious Adverse Event (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject using the automated system. The Sponsor or designee must be inf01med of the unblinding of a subject within 24 hours. All SUSARs will be unblinded by the Sponsor or designee for the purpose ofregulat01y rep01ting (see Section 9.2).

Eve1y reasonable attempt should be made to complete the early te1mination study procedures and observations (see Appendices A and B) prior to unblinding, as knowledge of the treatment ai·m could influence subject assessment.

In addition, the safety team assigned to review relevant Study Drng safety and tolerability data during the study in a blinded fashion will also have the ability to request the Ionis Drng Safety

Oversight Committee, chaired by the Chief Medical Officer, for unblinding the treatment assignment if needed for safety and data interpretation.

During the study, an unblinded interim analysis may be conducted to assess the safety and PK/PD results. The analysis will be executed with controlled dissemination of data to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study. Details of these controls will be described in the Statistical Analysis Plan (SAP).

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria during the Screening Period and must continue to meet up to prior to dosing on Study Day 1.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females aged 18 to 85 years old at the time of info1med consent
   a Females: must be non-pregnant and non-lactating and either:
      1. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);
      11. post-menopausal (defined as 12 months of spontaneous amenoIThea in females > 55 years of age or, in females :S 55 years, 12 months of spontaneous amenoIThea without an alternative medical cause and FSH levels in the postmenopausal range for the laborato1y involved); or,
      iii. if engaged in sexual relations and of child-beaTing potential, agree to use effective contraceptive methods (refer to Section 6.3.1) from the time of signing the infmmed consent form until at least 84 days (approximately 5 half-lives ofISIS 416858) after the last dose of Study Drng (ISIS 416858 or placebo).
   b Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the info1med consent form until at least 84 days (approximately 5 half-lives ofISIS 416858) after the la.st dose of Study Drng (ISIS 416858 or placebo).
3. End-stage renal disease maintained on outpatient hemodialysis at a healthcare center for > 3 months from screening with hemodialysis at least 3 times per week for a minimum of 9 hours per week of prescribed treatment time and plan to continue this throughout the study.

5.2 Exclusion Criteria

1. Subjects with a histo1y of a major medical event (e.g., previous acute corona1y syndrome, stroke or transient ischemic attack, or systemic thromboembolic event) within 3 months of screening, major surge1y within 3 months of screening, or new major physical examination finding (not accounted for by past medical history), except for documented AF.

2. Active bleeding (as judged clinically-significant by the Investigator) within the past 3 months from screening or documented bleeding diathesis (excluding uremia), coagulopathy, or recent history of prolonged compression time at arteriovenous fistula.
3. Screening laboratory results as follows:
   - Platelet count< 150,000 cells/mm^3
     - < 180,000 cells/mm^3 for platelet function/activation subgroup
   - INR > 1.4
   - aPTT > upper limit of normal (ULN)
   - FXI activity< 0.3 U/mL
   - ALTorAST>2xULN
   - Total bilirnbin > ULN
4. Subject is not willing to have weekly SC injections over the study period as assessed during screening.
5. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 (first dose) or IV antibiotic use at the time of screening.
6. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
7. Known histo1y of or positive test at Screening for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B.
8. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Subjects with a hist01y of other malignancies that have been treated with curative intent and which have no recunence within 5 years may also be eligible if approved by the Sponsor Medical Monitor (or designee).
9. Treatment with another investigational drug, biological agent, or device within one month of screening, or 5 half-lives of investigational agent, whichever is longer.
10. Any hist01y of previous treatment with an oligonucleotide (including siRNA). Subjects that have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration 2: 4 months has elapsed since dosing.
11. Attending nephrologist answers "no" to the question, "Would you be surprised if this patient died in the next year?"
12. Within 6 months prior to screening,
    - More than 3 episodes of severe hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
    - One (1) event of hypoglycemia in which the patient required hospitalization
    - Recunent syncope and recmTent hypotension in the inter-dialytic period requiring inte1vention

13. Planned major surgery in the next 6 months, including subjects receiving a kidney transplant or subjects that anticipate changing dialysis modality (i.e., hemodialysis to peritoneal dialysis).
14. Recent history of, or curTent drug or alcohol abuse as determined by the Investigator.
15. Concomitant use of anticoagulant/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, clopidogrel) that may affect coagulation (except low dose aspirin (:'.S 100 mg/day) during Treatment and Post-treatment Evaluation Periods is not allowed. Stable doses of heparins during dialysis are permitted.
16. Uncontrolled hypertension as judged by the Investigator. For example, patients with a pre- or post-dialysis blood pressure (BP) that is> 180 mmHg on at least 3 of the last 5 dialysis treatments.
17. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the study.

6. STUDY PROCEDURES

6.1 Study Schedule

The study period for an individual patient consists of a :'.S 4-week Screening Period for procedures followed by a 26-week Treatment Period, and a 12-week Post-Treatment Evaluation Period. Additional outpatient visits may be scheduled if required for further evaluation of an abnormal laboratory value or reported AE.

For patients participating in the PK substudy, there are 4 additional visits than those in the main study, occuning on Study Days 2, 177, 178, and 183. On Study Day 1 and at the end of the treatment period on Study Day 176, PK blood sampling is required at **1**, 2, 3, 4, 6, and 10 hours after Study Drug administration. Two (2) of the 4 additional visits may be on non-dialysis days (Study Days 2 and 177).

For patients participating in the platelet subgroup, no additional visits are required. Any AEs, concomitant medications, and other safety and tolerability profiling data will be promptly reported and reviewed by Sponsor's Medical Monitor (or designee).

All required study procedures are outlined in Appendices A, B, and C.

6.1.1 Screening

Day -49 to Day -14: Written informed consent for the study will be obtained prior to the performance of any study-related procedures.

Day-28 to Day-I: A:'.S 4-week period is provided to complete Screening assessments and procedures and to determine subject eligibility for the study. Subjects will be questioned for medical hist01y, and undergo physical examination, confomation of their ESRD status, 12-lead electrocardiogram (ECG), vital signs, body weight, and height. Race and ethnicity data will be collected as part of the demographic inf01mation for all screened subjects during the screening period.

Subjects will also be screened for infections of HIV, Hepatitis B and C, and for blood coagulation abnormalities including prolonged aPTT, PT, and international normalized ratio (INR), and low FXI activity levels(< 0.3 U/mL). All women will have a serum pregnancy test done between S-28 and S-14 that must be resulted prior to dosing on Study Day 1. Follicle-stimulating ho1mone (FSH) will be measured to confom menopause in women< 55 years of age that have 12 months of spontaneous amenonhea without an alternative medical cause. Additional blood samples will be taken for routine clinical laborato1y testing (Appendix A).

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to paliicipate in the study or continue with study procedures, all subjects will confom tolerance of SC administration prior to randomization. This injection will follow the same procedures as injections of the Study Drug (ISIS 416858 or placebo) during the treatment period. Specifically, during the screening period on Study Days S-14 (± 3) and S-7 (± 3), subjects should receive 2 noncontiguous SC injections of 0.75 mL saline within 2 hours after dialysis as described in Section 3.4.1.

The Screening results will be made available to decide individual subject's eligibility against inclusion/exclusion criteiia (Section 5.**1** and 5.2). Individual subjects will be disqualified if results of any laborat01y test are clinically-significant as judged by the Investigator or Sponsor's Medical Monitor (or designee). Eligible subjects will be emolled into the study.

6.1.2 Baseline (Day 1)

Baseline for the routine clinical assessments of chemistiy and hematology, PD markers, assessment of clotting, PK assessments, vital signs and ECG for the study will be the time-point prior to the first administi·ation of Study Drng and prior to dialysis on Day 1 (Appendix A). If Day 1 values are not available, screening values will be used. For Urea Reduction Ratio, the blood collections for blood urea niti·ogen (BUN) piior to dialysis as well as the post-dialysis sample on Day 1 will be used.

6.1.3 Treatment Period (Day 1 to Day 176)

Emolled subjects may be administered ISIS 416858 or placebo immediately after dialysis is completed (when blood is returning to the subject) but must be within 2 hours (preferably within 15 minutes) approximately once each week for a total of26 weeks ofb"eatment.

Once-weekly SC adminisb"ation will occur during Weeks 1 to 26 (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162, 169, and 176).

For Study Drug administi-ation on Study Day 1, no dosing window is allowed. For Weeks 2 to 26, a± 3-day window may be utilized but Study Drug should be administered each week. Study Drug doses should be administered at least 72 hours apart.

Additionally, no dose of Study Drug will be administered before reviewing a valid platelet result. Valid platelet counts must be conducted eve1y 2 weeks and reviewed prior to dosing. If the platelet result is unavailable (e.g., due to hemolysis, clumping, etc.) from the centi·al lab, a repeat local lab will be conducted and reviewed piior to dosing.

Any questions on study procedmes and visit windows may be directed to the Sponsor (or designee).

During all subject contacts, Investigators will check for and record:

- Bleeding events
- AEs
- Concomitant medication changes

Safety and clinical laboratory evaluations as well as PD markers, assessment of clotting, blood sampling, including those for routine PK as well as PK substudy analysis will be perfo1med as indicated in Appendices A, B, and C. Subjects pa1ticipating in the platelet substudy will have additional blood sampling and processing on Study Days 1, 78, and 176 during the Treatment Period.

Any AEs, including bleeding events, will be recorded. This may include additional info1mation regarding events of interest (i.e., thrombotic events).

6.1.4 Post-Treatment Evaluation Period

After completing the 26 weeks of the Treatment Pe1iod, subjects will return for follow-up visits as indicated in Appendix A. Patients will be followed until the Study Center visit on Day 260. Dming the Post-Treatment Evaluation Period, a visit window of± 3 days is allowed for Days 183, 190, and a visit window of± 7 days is allowed for visits between Days 204 and 260.

For all coho1ts, at all subject contacts, Investigators and staff will check for and record:

- Bleeding events
- AEs
- All concomitant medication changes

Safety and clinical laboratory evaluations as well as PD markers, assessment of clotting, blood sampling, including those for routine PK as well as PK substudy analysis, will be perfom1ed as indicated in Appendices A, B, and C. Subjects pa1ticipating in the platelet substudy will have additional blood sampling and processing on Study Day 260, the last day of the Post-Treatment Evaluation Period.

6.2 Study Assessments

6.2.1 Laboratory Assessments

Blood samples for clinical laboratory and PK assessments will be collected throughout the Study as detailed in Appendices A and C. A list of laboratory and PK analytes is contained in Appendix B.

6.2.2 Safety

Subjects with a suspected bleeding event will undergo additional testing if deemed appropriate by the treating physician and an (S)AE case report form will be completed. In addition, if

bleeding is considered significant, hemoglobin (Hb), hematocrit (Hct), aPTT, PT, INR, and platelet count are to be obtained, and approximately 2 mL of K2EDTA anticoagulated blood will be collected. The resulting plasma must be stored allowing for a centralized assessment of ISIS 416858 concentrations.

If the platelet value or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood specimen must be re-drawn as soon as possible (ideally within 7 days).

Subjects that withdraw from the study due to a change in dialysis modality or to undergo renal transplantation should notify the Sponsor Medical Monitor (or designee) and conduct the early termination procedures identified in Appendices A and C prior to the change or the surgery as appropriate. Whenever possible, a coagulation panel and PK blood sample should be collected prior to the initiation of renal transplant surgery. Additionally, at approximately 48 hours post-transplant, additional blood samples should be collected for Coagulation Panel (Appendix B) and ISIS 416858 plasma concentration (Appendix C). Any clinically-significant bleeding such as CRNMB and MB should be recorded and reported to the Sponsor Medical Monitor (or designee).

6.2.3 Clotting Assessments

Clotting assessments of the dialysis filter will be conducted throughout the Study as indicated in Appendix A. The clotting assessment will consist of a semi-quantitative scale by descriptive category (See Section 10.6.4) and will be performed by trained personnel.

6.3 Restriction on the Lifestyle of Subjects

6.3.1 Contraception Requirements

All male subjects and women of childbearing potential must refrain from sperm/egg donation and either be abstinentt or practice highly effective contraception from the time of signing the informed consent form until at least 12 weeks after their last dose of study treatment.

Male subjects engaged in sexual relations with a female of child-bearing potential must also encourage their female partner to use highly effective contraception from the time of signing the informed consent until 12 weeks after the subject's last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Postmenopausal: 12 months of spontaneous amenonhea in females > 55 years of age or, in females :S 55 years, 12 months of spontaneous amenonhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male subjects:

- Effective male contraception includes a vasectomy with negative semen analysis at Follow-up, or the use of condoms together with spennicidal foam/gel/film/ cream/suppositolY
- Male subjects with pa1tners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drng

For female subjects and female pa1tners of male subjects:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or ce1vical cap) together with spermicidal foam/gel/film/cream/suppositmy

tNote: Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

***Note: A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.**

7. STUDY DRUG

7.1 Study Drug Description

Study Drug (ISIS 416858 or placebo) characteristics are listed in Table 2.

The Study Drug (ISIS 416858 or placebo) is contained in 2 mL stoppered glass vials. The Study Drng (ISIS 416858 or placebo) and its storage and preparation instrnctions will be provided by the Sponsor or designee. The Study Drug (ISIS 416858 or placebo) must be stored securely at 2-8 °Celsius and be protected from light.

Table 2 Study Drug Charactel'istics

Study Drug	ISIS 416858	Placebo
Strength	200 mg/ml	Not Applicable
Volume	1 ml solution per vial	1 ml solution per vial
Route of Administration	Subcutaneous (SC)	Subcutaneous (SC)

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drng (ISIS 416858 or placebo) labeled in accordance with specific count1y regulato1y requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drng (ISIS 416858 or placebo) supplies provided by the Sponsor. The Study Center must return all used and unused Study Drng (ISIS 416858 or placebo) to the Sponsor or designee.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

Study Drng (ISIS 416858 or placebo) will be administered SC by trained personnel at the Study Center. Volumes to be administered are shown in Table 3. All doses of Study Drng will be administered after the completion of the hemodialysis treatment which can be while blood is returning to the patient but must be within 2 hours (preferably within 15 minutes of the conclusion of dialysis). Vials are for single use only. Please refer to the Study Drng Manual provided by the Sponsor (or designee) for more detailed instrnctions for Study Drng (ISIS 416858 or placebo) preparation and administration.

Table 3 Study Drug Dosing Information

Cohort	Volume to Administer	Number of Injections	Total Dose*
Cohort A (200 mg ISIS 416858 or placebo)	1.0 ml	1 of 1.0 ml	5200 mg ISIS 416858 or placebo
Cohort B (250 mg ISIS 416858 or placebo)	1.25 ml	1 of 0.75 ml and 1 of 0.5 ml	6500 mg ISIS 416858 or placebo
Cohort C (300 mg ISIS 416858 or placebo)	1.5 ml	2 of 0.75 ml	7800 mg ISIS 416858 or placebo

* Total dose of ISIS 416858 based on completed treatments for each cohort

8.2 Other Protocol-Required Drugs

A 0.9% sterile saline will be used for the SC tolerability injections pe1f01med during screening. At screening period Study Day S-14 (± 3) and S-7 (± 3), subjects should receive 2 noncontiguous SC injections of 0.75 mL saline to be administered following procedures for Study Drng as desclibed in Section 8.1.

8.3 Other Protocol-Required Treatment Procedures

Subjects are required to be receiving in center hemodialysis at least 3 times a week for a minimum of 9 hours per week while receiving Study Drng during the treatment period. Subjects no longer receiving the required in center hemodialysis should continue in the study with the regularly scheduled assessments, but will no longer receive Study Drng.

8.4 Treatment Precautions

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

Baseline for the routine clinical assessments of chemist:Iy and hematology, PD markers, assessment of clotting, PK assessments, vital signs and ECG for the study will be the last non-missing value prior to the first administt·ation of Study Drng and prior to dialysis on Day 1 (Appendix A). If Day 1 values are not available, screening values will be used.

For baseline Urea Reduction Ratio deternlination, the BUN blood collection prior to dialysis as well as the post-dialysis sample on Day 1 will be used.

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confumation Guidance: At any time during the study (Treatment or Post-Treatment Evaluation Periods), any clinical laborat01y results meeting the safety monitoring criteria presented below **must be confirmed** by perfo1ming measurements (ideally in the same laborat01y that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally witllin 7 days of the initial collection). For stopping rnles, if the initial laborato1y result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drng (ISIS 416858 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rnle must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rnles based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described in Sections 8.6.1, 8.6.2, or 8.6.3 are met, the subject will be permanently discontinued from further treatment with Study Drng (ISIS 416858 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rnles are adapted from the draft guidance for industry, "Drng-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drng Administt·ation, July 2009. For a defirlition of Baseline, please refer to guidance in Section 8.5 above.

In the event of an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement that is> 3 x ULN, or 3 x baseline value if the baseline value was> ULN at any time during the study (treatment and post-treatment evaluation periods), the initial measurement(s) should be confomed as described above. Additionally, confomat01y measurements should also be perfo1med if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements:

If the patient has confamed post-baseline ALT or AST levels> 3 x ULN, or 2 x baseline value, if the baseline value was> ULN at any time dming the study (treatment or post-treatment evaluation periods) that are continuing to rise, they should have their liver chemistry tests (ALT, AST, INR and total bilimbin) retested at least once-weekly until ALT and AST levels become :::; 1.2 x ULN or:::; 1.2 x baseline if the baseline value was> ULN.

Fmiher Investigation into Liver Chemistry Elevations:

For patients with confi1med ALT or AST levels> 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if baseline value was> ULN), the following evaluations should be perfo1med:

1. Obtain a more detailed history of symptoms and prior and concunent diseases
2. Obtain fmiher histo1y for concomitant dtug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational dtug use, and special diets
3. Obtain a histo1y for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (hepatitis A vims [HAV] IgM, hepatitis B surface antigen [HBsAg], hepatitis C vims [HCV] antibody, cytomegalovims [CMV] lgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography (CT) or magnetic resonance imaging (MRI) scans, may be perfmmed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor (or designee). Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 2: 5 x ULN.

8.5.2 Safety Monitoring Rules for Platelet Count Results

If a subject's absolute platelet count is 100,000/mm^3 or less, then the subject's platelet counts should be monitored weekly. In the event of a platelet count< 75,000/mm^3, additional laborato1y investigations may be conducted (Table 4). The frequency of monitoring and additional lab tests will be dete1mined by the Investigator in consultation with the Sponsor Medical Monitor (or designee).

Table 4 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

To Be Performed at Local Lab
Peripheral smear (should be perfom,ed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets Coagulation panel (PT/INR, aPTT) CBC with reticulocytes and mean platelet volume (MPV)
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo 819
Helicobacter pylori
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

8.5.3 Safety Monitoring for Bleeding Events

Subjects will be evaluated for occunence of bleeding events continuously after the start of Study Drug treatment (Day **1)** up to Day 260 for all cohorts. All bleeding events are considered AEs and reported on adverse event case report form.

Bleeding events that are either major or CRNMB (as defined below) will need to be monitored and treated immediately. Subjects with a suspected bleeding event will undergo additional testing if deemed appropriate by the treating physician and an (S)AE case report form will be completed. fu addition, if bleeding is considered significant, Hb, HCT, aPTT, PT, INR, FXI activity and antigen, and platelet count are to be obtained. fu addition, approximately 2 mL of

K2EDTA anticoagulated blood will be collected and resulting plasma must be stored allowing for a centralized assessment ofISIS 416858 concentrations.

In addition, if a minor bleeding event occurs, the Investigator should notify the Sponsor Medical Monitor (or designee) and additional testing of coagulation parameters (aPTT, PT, INR), platelet count, and platelet volume may be perfmmed.

Definitions:

Major bleeding (MB) is defined as one of the following:

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, ret:roperitoneal, intraaiiicular if in a major joint, or pericardia!, or intramuscular with compaiiment syndrome
3. Clinically ove11 bleeding leading to transfusion of 2 units of packed red blood cells or whole blood or a fall in Hb of 20 g/L (1.24 mmol/L) or more within 24 hours

Clinically-Relevant Non-Major Bleeding (CRNMB) is defined as ove1t bleeding not meeting the critelia for MB but that resulted, for example, in medical examination, inte1vention, or had clinical consequences for a subject (Biiller et al. 2007).

Minor bleeding events are those that do not fulfill the cliteria for MB or CRNBM events (defined above), for example excess bruising, petechiae, gingival bleeding on brnshing teeth.

8.6 Stopping Rules for Study Drug

When stopping rnles are met for liver chemistry elevations, platelet count reductions, or bleeding events, then Study Drng administr·ation must be discontinued. However, subjects are encouraged to continue with study assessments through the tr·eatment and post-tr·eatment evaluation periods, but will no longer receive Study Drng.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of confamed laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor (or designee),** dosing of a patient with Study Drng (ISIS 416858 or placebo) will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confamed:

1. ALT or AST> 8 x ULN, which is confi1med
2. ALT or AST> 5 x ULN, which is confi1med and persists for 2weeks
3. ALT or AST> 3 x ULN (or the greater of2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confi1med and total bilirnbin > 2 x ULN or INR > 1.5)

4. ALT or AST> 3 x ULN (or the greater of2 x baseline value or 3 x ULN if the baseline value was> ULN), which is confi1med, **and** with the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2 Stopping Rule for Platelet Count Reduction

In the event of a confi1med platelet count less than 75,000/mm^3, dosing of a subject with Study Drng (ISIS 416858 or placebo) will be stopped permanently. Fmthe1more, additional laborato1y investigations will be conducted as outlined in Table 4. The platelet count should be tested weekly until it is above 100,000/mm^3. The subsequent follow-up schedule for any events meeting this stopping criterion will be dete1mined by the Investigator in consultation with the Sponsor Medical Monitor (or designee).

In the event of a platelet count< 50,000/mm^3, the Sponsor must be notified within 24 hours and platelets are to be monitored daily until 2 successive values show improvement, then monitored every 2-3 days until the platelet count is stable. A stable platelet count is considered when at least 6 consecutive values measured are> 100,000/mm^3 with no downward trend as dete1mined by the Sponsor Medical Monitor (or designee). It is recommended that the subject receive glucoco1ticoid therapy to accelerate the recovery in the platelet decline (strongly recommended if platelet count< 25,000/mm^3). To optimize patient treatment, a discussion between the Investigator and the Sponsor Medical Monitor (or designee) must occur. Treatment guidelines for inllllune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days eve1y 2-4 weeks for 1-4 cycles; prednisolone 0.5-2 mg/kg/day for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days **(note:** may require continuation with oral cmticosteroids after methylprednisolone).

8.6.3 Stopping Rule for Bleeding

If an event of Major Bleeding or CRNMB event occurs, the Investigator must notify the Sponsor Medical Monitor (or designee) and the subject should be closely monitored (vital signs, lab tests such as Hb, HCT and platelet count, additional outpatient visits, overnight stays and coagulation tests may be needed) throughout the treatment and during the post-treatment evaluation period.

In the event of Major Bleeding or CRNMB (see definitions in Section 8.5.3) as assessed by the Investigator, dosing of a subject with Study Drng (ISIS 416858 or placebo) may be stopped permanently. The follow-up schedule for any events meeting this discontinuation criterion will be dete1mined, including the suitability of the subject for resumption of dosing by the Investigator in consultation with the Sponsor Medical Monitor (or designee).

Treatment Precautions:

Recommendations to manage bleeding in a patient will be provided to all study sites:

Specifically, if a patient has Major Bleeding or Clinically Relevent Non-Major Bleeding during the trial, the following measures are to be considered by the Investigators to control that bleeding:

1. Delay of the next injection or discontinuation of treatment in consultation with Sponsor Medical Monitor (or designee) per Section 8.6.3.
2. Review and discontinue concomitant medications that could exacerbate bleeding.
3. Mechanical compression/ Surgical inte1vention/haemostasis.
4. General volume management: fluid replacement & hemodynamic suppo1t.
5. Transfusion (whole blood/packed cells/FFP/platelets).

If bleeding cannot be controlled by these measures, consider administration of one of the following procoagulants (according to the dosages advised in the package inse1t), FXI concentrate (Hemoleven®), Recombinant Factor Vila (NovoSeven®), or 4-factor concentrate (prothrombin complex concentrate).

ISIS 416858 treatment does not directly inhibit circulating FXI, only production of this clotting factor in the liver. Therefore, the dose of fresh frozen plasma (FFP) or factor concentrate given should aim to increase FXI activity above 0.3 U/mL and should recognize that the half-life of circulating FXI is approximately 50 hours when considering the potential need for re-administration. Additionally, the time necessa1y to obtain a FXI concentration locally and to infuse FFP should be taken into consideration.

8.7 Discontinuation of Study Drug

A subject must pe1manently discontinue Study Drug (ISIS 416858 or placebo) for any of the following:

- The subject becomes pregnant. Repo1t the pregnancy according to instmctions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an AE that necessitates permanent discontinuation of Study Drug
- The subject develops laborato1y test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.3
- The subject experiences an AE that necessitates unblinding of the Investigator to the subject's treatment assignment
- The subject is no longer on maintenance hemodialysis of at least 3-times per week for a minimum of 9 hours per week which includes a change in dialysis modality or renal transplantation
- The subject begins treatment with a disallowed concomitant medication as described in Section 8.9.1

The reason for discontinuation of Study Drug must be recorded in the electronic Case Rep01t F01m (eCRF) and source documentation. Every effort should be made to complete the early termination study procedures and obse1vations as detailed in Appendix A at the time of withdrawal.

Subjects who discontinue Study Drug are encouraged to remain in the study. Subjects that discontinue treatment such as in cases where hemodialysis is held for > 2 weeks or stopped, or there is a change of dialysis modality (i.e., hemodialysis to peritoneal dialysis) or receive a renal transplant (See Section 6.2.2) are encouraged to complete the treatment and the post-treatment evaluation period visits unless consent is withdrawn.

If the subject declines or is unable to participate in the post-treatment evaluation period, the fuvestigator should clarify what type of follow-up the subject is agreeable to, such as by telephone or through their treating physicians. At the very least, the subject's status at the end of the protocol defined study period should be asce1tained and documented wherever possible. The agreed means of follow-up should be documented in the subject's records and notified to the Sponsor.

8.8 Withdrawal of Subjects from the Study

Subjects must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The subject is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the Study might include:

- At the discretion of the fuvestigator for medical reasons
- At the discretion of the fuvestigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF. Any subject who withdraws consent to pa1ticipate in the study will be removed from further treatment and study obse1vation immediately upon the date of request. These subjects should be encouraged to complete the early termination study procedures and obse1vations at the time of withdrawal (Appendix A).

For subjects withdrawn for reasons other than withdrawal of consent every effo1t should be made to complete the early termination study procedures and observations at the time of withdrawal (see Appendix A).

8.9 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.9.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified mug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between the signing of informed consent and the last protocol specified Post-Treatment Evaluation Period visit (Appendix A).

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy. The use of stable doses of unfractionated heparin and low-molecular weight heparin during hemodialysis is allowed.

Disallowed Concomitant Therapy

Concomitant use of anticoagulant/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, clopidogrel) that may affect coagulation (except low dose aspirin(:::;100 mg/day) during Treatment and Post-treatment Evaluation Periods is not allowed.

For subjects in the platelet function/activation subgroup, use of any anticoagulants or antiplatelet agents (other than aspirin) is not allowed.

8.9.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and last protocol-specified Post-Treatment Evaluation visit (Appendix A).

8.10 Treatment Compliance

Compliance with Study Drng dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety infom1ation will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the Safety Management Plan and Medical Monitoring Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any SAE according to applicable regulations.

In addition to the Investigator's assessment of relatedness of SAEs to the Study Drug, the Sponsor or designee will evaluate the available information and perform an independent causality assessment of all reported SAEs. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the pmpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

9.3 Definitions

9.3.1 Adverse Event

An adverse event (AE) can be any unfavorable and unintended sign (including an abn01mal laborato1y finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

Adverse events are to be identified between study visits by evaluating components of the medical record that contain valid and verifiable claims about a medically untoward event. For hemodialysis subjects, this includes a complete review of changes in the dialysis prescription in the dialysis chaii orders section or inf01mation provided to the study staff directly by the subject. Dialysis treatment summaries (rnn-sheets) should be reviewed for pertinent information when indicated.

9.3.2 Adverse Drug Reaction and Unexpected Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).

An unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

9.3.3 Serious Adverse Event (SAE)

A SAE is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occmTence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occuned in a more severe fo1m, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 homs to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disrnption of the ability to conduct normal life functions

- Results in a congenital anomaly or bi.Ith defect in the offspring of the subject (whether the subject is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result **in** inpatient hospitalization, or the development of drug dependency or drug abuse

9.3.4 Adverse Event of Interest

Adverse events of interest (AEol) includes both serious and non-serious events of MB and CRNMB, defined in Section 8.5.3 (Safety Monitoring for Bleeding Events).

AEol are required to be reported by the Investigator to the Sponsor immediately, no more than 24 hours of the Investigator's first knowledge of the event.

9.4 Monitoring and Recording Adve1·se Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened to an extent not consistent with the natural history of the condition.

In subjects with ESRD requiring dialysis, events due to abnormalities of serum electrolytes such as sodium, potassium, chloride, bicarbonate, calcium, and phosphorus, the anemia of chronic disease, and hypertension are considered pa1t of their underlying condition. In addition, mechanical complications of vascular accesses are common in subjects that requiI·e dialysis. Events that are consistent with the natural history ofESRD and the need for dialysis will not be considered AEs unless theiI·course or severity is atypical for this population or thought potentially due to the Study Drug (e.g., due to bleeding) in the opinion of the Investigator. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Reporting Requirements for Serious Adverse Events Using Electronic Case Report Forms (eCRFs)

In the interest of subject safety, and in order to fulfill regulato1y requiI·ements, all SAEs (regardless of their relationship to Study Drug) should be repo1ted to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. Similarly, all events that meet the criteria for Major or CRNMB (see definitions in Section 8.5.3) must also be repo1ted within 24 hours of the Study Center's first knowledge of the event.

The collection of SAEs and Clinically-Relevant Bleeding events will begin after the subject signs the info1med consent fo1m and stops at the end of the subject's follow-up period which is defined as the last protocol specified Post-Treatment Evaluation Period visit. A SAE should be repo1ted using the electronic SAE submission fo1m whenever possible. In situations where the

electronic SAE submission is unavailable and the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message.

For events that occur prior to Study Drng initiation, the Serious Adverse Event Reporting Form provided to Investigators should be completed and submitted to Ionis or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing (using the fax cover sheet provided to Investi ators with countr -s ecific fax numbers) or by scanning and emailing the form to [redacted]

For events that occur after Study Drng initiation, Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report should be automatically generated and sent to Ionis or designee by the EDC system.

In the event that the EDC system is unavailable, the **Serious Adverse Event Reporting Form** provided to Investigators should be completed and submitted to Ionis or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing (using the fax cover sheet provided to Investi ators with countr -s ecific fax numbers) or by scanning and emailing the form to Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol specified Post-Treatment Evaluation visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree that the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as the last protocol specified Post-Treatment Evaluation Period visit. The Investigator will monitor each subject closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form.

9.4.3.1 Relationship to the Study Drug

The event's relationship to the Study Drng (ISIS 416858 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drng, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drng (ISIS 416858 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drng (ISIS 416858 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drng (ISIS 416858 or placebo)

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Te1minology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities
- **Moderate:** The event causes the subject more discomfo1t and intenupts the subject's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities

If the event is a SAE, then **all** applicable seriousness cliteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drng (ISIS 416858 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drng (ISIS 416858 or placebo) administration and dose
- **Permanently Discontinued:** Study Drng was discontinued and not resta1ted
- **Temporarily Interrupted, Restarted- Same Dose:** Dosing was temporarily intenupted or delayed due to the AE and restarted at the same dose

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Repo11 Fonn. Treatment should also be recorded on the concomitant treatment or ancilla1y procedures eCRF, as appropriate.

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- **AE Persists:** Patient te1minates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became se1ious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the conesponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is a SAE, then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious c1iteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recove1y should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abno1mal laborato1y test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abno1mal laborat01y results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac anhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abno1mal laborat01y values as AEs. Clinically-significant abn01malities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor (or designee). Laboratory abn01malities deemed not clinically-significant (NCS) by the Investigator, or those associated with hemodialysis or ESRD (e.g., asymptomatic inild to moderate hyperkalemia, hyperphosphateinia, etc.) should not be repoded as AEs. Siinilarly, laborato1y abno1malities repoded as AEs by the Investigator should not be deemed NCS on the laborato1y sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abn01mal laborat01y values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered a SAE, even if the subject is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to paiticipate in the study and the timing of the procedure or t1eatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Study Drng (ISIS 416858 or placebo) enorsshould be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Rep01t F01m. If the subject takes a dose of Study Drng (ISIS 416858 or placebo) that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Subjects must continue to use appropriate highly effective contraception with their paitners, or refrain from sexual activity, as described in Section 6.3.1.

If a subject becomes pregnant or a pregnancy is suspected, or if a male subject makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first leaining of the occmTence of pregnancy. Follow-up inf01mation including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy F01ms and rep01ted within 24 hours.

Payment for all aspects of obstetrical cai·e, child or related care will be the subject's responsibility.

Female subjects: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be perf01med. The subject with a confamed pregnancy will be immediately withdrawn from treatment with Study Drng. However, the subject will be encouraged to complete the post-treatment follow-up p01iion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study pa1iicipation, the study physician will assist the subject in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delive1y, elective te1mination, or spontaneous abo1iion). If the pregnancy results in the bilih of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional info1mation relevant to the pregnancy outcome. Follow-up will be performed to the extent pe1mitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male subjects: The progress of the pregnancy of a male subject's paiiner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abo1iion). If the pregnancy results in the bi1ih of a child, **the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy and the newborn child.** Follow-up will be perf01med to the extent permitted by the applicable regulations and privacy considerations, e.g., paliner ICF may be required.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Safety and Tolerability

The primaiy safety outcome is the combination of MB and CRNMB during the treatment period (or early study terniination). For the subgroup of subjects evaluated for platelet function and/or activation, an analysis of pre- and post-treatment results with ISIS 416858 may be conducted and compared to treatment with placebo.

The safety and tolerability of ISIS 416858 will be accessed by dete1mining the incidence and severity of AEs and will be evaluated by reviewing:

- AEs (including bleeding events)
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Coagulation parameters
- Use of concomitant medications

10.1.2 Pharmacodynamic Outcomes

- Change from Baseline in FXI antigen and activity
- Change from Baseline in aPTT
- The extent and frequency of clotting on the dialysis filters and circuit

10.1.3 Exploratory Outcomes

- Incidence of myocardial infarction (MI), stroke, systemic embolism, and cardiovascular (CV) mortality

10.1.4 Other Study Outcomes and Evaluations

- Urea Reduction Ratio
- PK

10.2 Sample Size Considerations

The sample size was selected based on prior experience to ensure that the safety, tolerability and PK/PD relationships will be adequately assessed while minimizing unnecessary patient exposure. There is no statistical rationale for the selected sample size.

10.3 Populations

Intent to Treat Population: All subjects randomized who have received at least 1 dose of Study Drng.

Per Protocol Population: All subjects who are randomized without missing more than 2 doses during the first 12 weeks or more than 5 doses over the 26-week Treatment Period and who do not have any major protocol violations that would affect the interpretation or integrity of the study results.

Safety Population: All subjects randomized who have received at least 1 dose of Study Drng.

PK Population: All subjects who have received at least 1 dose of active Study Drng (ISIS 416858), and have at least 1 PK sample collected and analyzed with evaluable results.

10.4 Definition of Baseline

Baseline for the routine clinical assessments of chemist:Iy and hematology, PD markers, assessment of clotting, PK assessments, vital signs and ECG for the study will be the last non-missing value prior to the first administration of Study Drug (ISIS 416858 or placebo) and prior to dialysis on Day 1 (Appendix A). If Day 1 values are not available, screening values will be used. For Urea Reduction Ratio, the BUN blood collections prior to dialysis as well as the post-dialysis sample on Day 1 will be used to establish baseline.

10.5 Interim Analysis

No interim analysis is planned. However, dming the study, an unblinded interim analysis may be conducted to assess the safety, PK/PD, and explorato1y efficacy of the results. The analysis will be executed with conti·olled dissemination to ensme the integiity of ongoing data collection

while maintaining sufficient blinding in the study. Details of these controls will be described in the SAP.

10.6 Planned Methods of Analysis

Descriptive summary analysis including mean, median, standard deviation, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

Safety and PD assessments will be performed on the Safety population. Exploratory efficacy and clotting assessment measures may be assessed on the Per Protocol population.

10.6.1 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by tTeatment group. Subject randomization will be summarized by treatment group. The subject disposition will be summarized. All subjects emolled will be included in a summa1y of subject disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drng (ISIS 416858 or placebo) received will be summarized by treatment group. Subject incidence rates of all AEs will be tabulated by the Medical Dictionary for Regulato1y Activities (MedDRA™) system organ class, and by MedDRA™ te1m. Tables and/or nanatives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drng, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drng (ISIS 416858 or placebo) will be summarized.

Laborato1y tests to ensure subject safety including chemistly panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each ti·eatment group. These safety va1iables will also be presented as change and percent change from Baseline over time after Study Drng (ISIS 416858 or placebo) administi·ation, as approp1iate.

Vital sign and ECG measures will be tabulated by ti·eatment group. In addition, the number of subjects who experience abn01malities in clinical laboratory evaluations will be summarized by ti·eatment group.

Incidence of bleeding events including the following will be tabulated by treatment:

- MB
- CRNMB
- Minor bleeding
- Combination of MB and CRNMB

Physical examination data will be provided in the data listing. Concomitant medications will be coded using World Health Organization (WHO) Drng dictionruy and summarized by treatment, ATC class and generic name.

10.6.3 Pharmacokinetic and lmmunogenicity Analysis

10.6.3.1 Pharmacokinetic Analysis

Noncompa1tmental PK analysis ofISIS 416858 will be catTied out on each individual subject data set in the PK subgroup where plasma PK will be assessed following the first dose (single-dose PK) and last dose (steady-state PK) ofISIS 416858, whenever possible. The maximum observed mug concentration (Cmax) and the time taken to reach Cinax (Tmax) will be obtained directly from the concentration-time data. Partial areas under the plasma concentration-time curve from time zero (pre-dose) to the last observable concentration (AUCo-t) and dosing interval (AUC0-16shr) after SC administration of ISIS 416858 will be calculated using the linear-up log-down trapezoidal rnle. Apparent systemic (plasma) clearance at steady state after SC administration (CL.JP) will be calculated from CL.JP= Actual Dose/AUC0-16shr-

For all evaluable subjects receiving ISIS 416858, plasma ISIS 416858 concentrations at trough during the Treatment Period and concentrations observed during the Post-Treatment Evaluation Period will be listed by dose, study day, time point, subject ID, anti-drug antibody (ADA) status, and summru·ized using descriptive statistics. The apparent plasma terminal elimination half-life ofISIS 416858 following the last administered dose will be calculated in each evaluable subject (when deemed possible by the PK scientist).

Plasma PK parameters will be summarized using descriptive statistics. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Additional details regru·ding the PK analysis will be described in the SAP.

Potential relationships between selected PD and plasma exposure measures (e.g., trough concentrations) may also be explored, where deemed appropriate.

10.6.3.2 lmmunogenicity Analysis

Immunogenicity results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-ISIS 416858 antibodies) before, during, and after treatment with Study Drug (ISIS 416858) (i.e., sample ADA status) will be listed. Subject ADA status (positive/negative or not evaluable) for all evaluable subjects, along with the study day that the first positive immunogenicity status emerged (Ttust, i.e., onset of ADA development), the last positive immunogenicity status observed (T1ast), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their treatment and study day. Subjects with positive anti-ISIS 416858 antibody status may be further classified (where applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject immunogenicity incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment and dose. Fmthermore, onset, titer over time, and peak titer of the ADA response, if applicable, will be summa1ized as median, quartiles (25% and 75%), and range by treatment and dose.

Additional details regarding the IM data analysis will be described in the SAP.

10.6.4 Pharmacodynamic Analysis

Pharrnacodynamic analyses will be perfmmed in the safety population. Change and percent change in FXI activity and antigen levels, aPTT, PT, and INR will be tabulated over time.

The extent and occmrence of clotting on the dialysis filters and circuit will be summarized descriptively by categmy scoring.

Table 5 Clotting Scale

Inspection Site	Category 1	Category 2	Category 3	Category4
Air Trap	No clotting	Fibrinous ring with no clot formation on venous chamber filter	Clot formation on venous chamber	Coagulated system (treatment cannot continue without new setup)
Dialyzer	Clean dialyzer	Blood stripes affecting less than 5% of the fibers seen at the surface of the dialyzer	Blood stripes affecting 5% or more of the fibers seen at the surface of the dialyzer	Coagulated filter

Note: Overall score is the highest of the individual component scores

The relative occmTence of each clotting category will also be summarized from all obtained clotting assessments, whenever possible. Further details on the analysis of clotting assessments will be contained in the SAP.

10.6.5 Additional Exploratory Analyses

Incidence of myocardial infarction (MI), stroke, systemic embolism, and cardiovascular (CV) mmtality will be explored.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English Version provided by the Sponsor or designee.

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drng (ISIS 416858 or placebo) are administered. The subject must be given sufficient time to consider whether to pa1ticipate in the study.

The acquisition of informed consent and the subject's agreement or refusal to notify his/her primary care physician should be documented in the subject's medical records and the infmmed consent form should be signed and personally dated by the subject and by the person who conducted the infmmed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations

required by institutional policy, and a copy of the signed consent form should be provided to the subject.

11.2 Ethical Conduct of the Study

All applicable regulations and guidelines of cunent Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatmy requirements must be followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed infonned consent fo1ms, other written subject info1mation, and any proposed adve1tising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent fo1m must be received by the Sponsor or designee before recruitment of subjects into the study and shipment of Study Drug (ISIS 416858 or placebo). A copy of the written approval of any other items/materials that must be approved by the Study Center or IRB must also be received by the Sponsor or designee before recruitment of subjects into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the inf01med consent document. The Investigator should notify the IRB of deviations from the protocol in accordance with ICH E6 Section 4.5.2. The Investigator should also notify the IRB of SAEs occmTing at the Study Center and other AE repmts received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the Investigator's repmts, all IRB submissions and the IRB continuance of approval must be sent to the Sponsor or designee.

11.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case repmi fmms or other documents submitted to the Sponsor or designee, subjects should be identified by initials (if pe1mitted by local law) and a subject identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed info1med consent fmms) should be kept in strict confidence by the Investigator.

In compliance with ICH E6, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and repo1ts that are impo1tant to the evaluation of the study. The Investigator is obligated to info1m and obtain the consent of the subject to pe1mit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the fuvestigator must be obtained for all protocol amendments and amendments to the infonned consent document. The regulat01y authority and IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The fuvestigator **must** send a copy of the approval letter from the IRB to the Sponsor or designee.

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The fuvestigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The fuvestigator/Sponsor or designee should notify the IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3 Study Documentation and Storage

An eCRF utilizing an EDC application will be used for this Study.

The fuvestigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the subject's case rep01t form data are obtained. These include but are not limited to hospital records, clinical and office charts, laborat01y and pharmacy records, imaging, and conespondence.

The fuvestigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH E6, suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulat01y authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supp01ting copies of source documentation
- Study files containing the protocol with all amendments, fuvestigator's Brochure, copies of pre-study documentation and all conespondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Sh1dy Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related coITespondence

fu addition, all original source documents supporting entries in the case rep01i forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the fuvestigator. Should the Investigator wish to assign the study records to another pa1ty or move them to another location, he/she must notify the Sponsor or designee.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the va1ious records of the hial (e.g., case report fo1ms and other pe1tinent data) provided that subject confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case repo1t fo1ms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to ve1ify the entries on the case repmt forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case repmt fo1ms, are resolved.

In accordance with ICH E6 and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Depa1tment (or designees). Inspection of Study Center facilities (e.g., pha1macy, drng storage areas, laboratolies) and review of study-related records will occur to evaluate the h"ial conduct and compliance with the protocol, ICH E6, and applicable regulato1y requirements.

To ensure the quality of clinical data a clinical data management review will be perfo1med on subject data received by the Sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case repo1t fo1m. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report fmm, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report fo1ms must be completed in English. Generic and ti·ade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name in English if possible.

All wlitten info1mation and other material to be used by subjects and investigative staff must use vocabulaiy and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains approp1iate insurance coverage for clinical h"ials and will follow applicable local compensation laws. Subjects will be ti·eated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injmy section of the Infmmed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

SCREENING				
	Informed Consent (Must be signed before any Screening Procedures)	**Screening Period Procedures** (28 **Days)**		
	S-49 to S-14	**S-28 to S-14**	**S-14**	**S-7**
Visit Window (Days)			±3	
Informed Consent	X			
Inclusion/Exclusion		X		
Medical History		X		
HIV, Hepatitis B & C		X		
FSH[1]		X		
Serum Pregnancy[2]		X		
Body Weight and Height (Height at Screening only)		X		
Physical Exam		X		
Vital Signs[3,4]		X		
ECG (12-Lead)		X		
Chemistry Panel[5]		X		
Hematology5		X		
Coagulation Panel		X		
Inflammatory Panel		X		
Adverse Events	X	X	X	X
Concomitant Medications	X	X	X	X
Assessment of clotting[6]		X		
SC Tolerability Assessment[7]			**X**	X

Appendix A Schedule of Procedures *Continued*

	Treatment Period (26 Weeks)																			
	W1 D1	**W1 02•**	**W1 D5**	**W2 D8**	**W2 D12**	**W3 D15**	**W4 D22**	**W5 D29**	**W6 D36**	**W7 D43**	**W8 D50**	**W9 D57**	**W10 D64**	**W11 D71**	**W12 D78**	**W13 D85**	**W14 D92**	**W15 D99**	**W16 D106**	**W17 D113**
Visit Window (Days)	0		±3																	
Inclusion/Exclusion	X																			
Serum Pregnancy[2]															X					
Body Weight and Height (Height at Screening only)													X							
Physical Exam				X				X					X							
Vital Signs[3,4]	X	x•.11	X	X	X	X	X	X	X4	X	X	X	X	X	X4	X	X	X	X	X
ECG (12-Lead)	X							X							X					
Chemistry Panel[5]	X		**X**		**X**	X	X	X	X		X		**X**		X		X		**X**	
Urea Reduction Ratio, Kt/VS	XA,B								XA,B				XA,B				XA,B			
Hematology[5]	**X**		**X**		**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**		**X**		**X**	
Coagulation Panel	**X**		X		X	**X**	**X**	**X**	**X**		X		X		**X**		**X**		X	
Inflammatory Panel	**X**					**X**		**X**			X				X				X	
Platelet Function/Activation Test9	X														X					
Study Drug Administration[10]	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	x•.11	X	X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	**X**	X	X
Concomitant Medications	X	x•.11	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**
Assessment of clotting[6]	X			X		**X**		**X**		**X**		X		**X**		**X**		**X**		**X**
PK Blood Sampling[11]	XA,11	X*.A.1		XA				XA				XA				XA				XA
Immunogenicity	XA					XA		XA								XA				

Appendix A Schedule of Procedures *Continued*

	Treatment Period (26 Weeks) *Continued*												Post-Treatment Evaluation Period (12 Weeks)							
	W18 D120	W19 D127	W20 D134	W21 D141	W22 D148	W23 D155	W24 D162	W25 D169	W26 D176	W26 D177	W26 D178	Early Term Tx	W27 D183	W28 D190	W30 D204	W32 D218	W34 D232	W36 D246	W38 D260	Early Term FU
Visit Window {Days)	±3												±3		±7					
Serum Pregnancy[2]									X			X							X	X
Body Weight	X								X			X							X	X
Physical Exam	X								X			X				X			X	X
Vital Signs[3,4]	X4	X	X	X	X	X	X4	X	X			X		X	X4	X	X	X4	X	X
ECG (12-Lead)									X			X							X	X
Chemistry Panel[5]	X		X		X		X		X			X		X	X	X	X	X	X	X
Urea Reduction Ratio, KW[8]	XA,B				XA,B				XA,B			XA,B			XA,B		XA,B		XA,B	XA,B
Hematology5	X		X		X		X		X			X		X	X	X	X	X	X	X
Coagulation Panel	X		X		X		X		X			X		X	X	X	X	X	X	X
Inflammatory Panel			X				X		X			X			X		X		X	X
Platelet Function/Activation Test[9]									X			X							X	
Study Drug Administration[10]	X	X	X	X	X	X	X	X	X											
Adverse Events	X	X	X	X	X	X	X	X	X	x·,11	x•.11	X	x•.11	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	x•.11	x•.11	X	x•.11	X	X	X	X	X	X	X
Assessment of clotting[6]	X		X		X		X		X					X	X	X	X	X	X	X
PK Blood Sampling[11]					XA				XA	X*,A,11	X*,A,1	XA	X*,A,11	XA	XA		XA		XA	XA
Immunogenicity									XA			XA							XA	XA

Appendix A Schedule of Procedures *Continued*

Notes: -If not specifically labeled, "X" means Pre-dialysis. Please refer to Appendix C for PK blood sampling procedures. A 10-minute time window applies to all procedures to allow for flexibility where multiple procedures are scheduled at the same time-Subjects who terminate the study early should complete the procedures indicated for the early term visit (Treatment or Post-Treatment Evaluation Period). For subjects that undergo renal transplant, please refer to Section 6.2.2.

* Only applies to PK subgroup participants

1 Women!, 55 years who are not surgically sterile and have 12 months of spontaneous amenorrhea as confirmation of menopause

2 For all women, to be done once at S-28 to S-14. For women of child bearing potential who are not surgically sterile, a serum test at all time points after Day 1

3 BP, HR, RR, temp

4 BP at selected visits will be assessed 3 times, approximately 5 minutes apart

5 If the platelet value or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days) and reviewed prior to dosing. Valid platelet counts must be conducted every 2 weeks and reviewed prior to dosing

6 The rate/frequency of clotting on the dialysis filters and circuit will be measured as an exploratory PD analysis

7 At screening Study Day S-14 (± 3) and S-7 (± 3), subjects should receive 2 noncontiguous SC injections of 0.75 ml saline. This injection will follow the same procedures as injections of the Study Drug (ISIS 416858 or placebo) during the treatment period. Specifically, during the screening period on Study Days S-14 (± 3) and S-7 (± 3), subjects should receive 2 noncontiguous SC injections of 0.75 ml saline immediately after dialysis when blood is returning to the subject but must be within 2 hours after dialysis (preferably within 15 minutes of the conclusion of dialysis)

8 Urea Reduction Ratio is a measure of serum BUN, collected before and just after dialysis, and is used to estimate the reduction in urea as a result of dialysis as a measure of efficiency of the dialysis procedure. In addition, the subject's most recent KW value, preferably single-pooled Kt/v if possible will be collected directly from the subject's chart

9 Platelet Function/Activation Subgroup Subjects only (approximately 12 subjects selected from each cohort), please refer to Section 3.1.1

10 Study Drug will be administered SC after completion of hemodialysis which can be as soon as blood is returning to the patient but must be within 2 hours (preferably within 15 minutes of the conclusion of dialysis)

11 Please refer to Appendix C for PK sampling procedures. For PK Subgroup Subjects (approximately 12 subjects selected from each cohort), please refer to Section 3.1.2 and Appendix C for PK subgroup sampling procedures

Time:

A Pre-dialysis

B Post-dialysis

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 416858 or other similar oligonucleotides.

Additional Labs that May Be Perfo1med in the Event of a Platelet Count< 75,000/mm^3 are listed in Section 8.5.2.

Chemistry Panel	**Other Tests**	Hematology
Total protein	Hepatitis B surface antigen	Red blood cells
Albumin	Hepatitis C antibody	Hemoglobin
Glucose	HIV antibody	Hematocrit
Total bilirubin	FSH (women 55 years with 12 months of spontaneous amenorrhea only)	MCV, MCH, MCHC
Direct (conjugated) bilirubin	Serum Pregnancy test	Platelets
Indirect (unconjugated) bilirubin	**Inflammatory Markers**[1]	• Count and Volume (MPV) (All Subjects)
ALT	Hs-CRP	• Function and/or Activation (Subgroup Subjects only)
AST	D-dimer	White blood cells (WBC)
GGT	Beta-2-M	WBC Differential
Urea Reduction Ratio	Cardiac troponin I and T	(% and absolute)
BUN	NT-proBNP	Neutrophils
	Coagulation PaneP	Eosinophils
	aPTT (sec)	Basophils
	PT (sec)	Lymphocytes
	INR	Monocytes
	FXI antigen level and activity	**Pharmacokinetics and Immunogenicity**
		ISIS 416858 levels in plasma[2]
		Anti-ISIS 416858 antibodies

1 Other biomarkers may be measured, as needed; at the discretion of the Sponsor, samples will be collected and stored

2 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation), or to assess other actions of !SIS 416858 with plasma constituents or PD biomarkers

3 Coagulation panel analytes are to be blinded except at Screening

Appendix C PK Sampling Schedule

PK Sampling Schedule for All Subjects:

Period	Treatment (26 Weeks)								Post-Treatment Evaluation (12 Weeks)			
Week	W1	W2	W5	W9	W13	W17	W22	W26	W28	W30	W34	W38
Study Day	D1	D8	D29	D57	D85	D113	D148	D176	D190	D204	D232	D260
Blood Sampling Time	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis	Pre-dialysis

Additional PK Sampling Schedule for PK Subgroup Only:

D1	D2	D176	D177	D178	D183
Blood: First sample Pre-dose (taken pre-dialysis) and rest of samples Post SC injection at 1, 2, 3, 4, 6, and 10 hours Post SC Injection	Blood: 24-hour post the D1 dose (pre-dialysis)	Blood: First sample Pre-dose (taken pre-dialysis) and rest of samples Post SC injection at 1, 2, 3, 4, 6, and 10 hours Post SC Injection	Blood: 24-hour post D176dose (pre-dialysis)	Blood: 48-hour post D176dose (pre-dialysis)	Blood: 168-hour post D176dose (pre-dialysis)

Note: PK Subgroup subjects will also complete all the regularly scheduled visits and PK sampling schedule
The regular visit Day 8 PK sample constitutes the 168-hour sample for Day 1 of the PK Subgroup

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the Common Te1minology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010.

Adve.-se Event	**Mild**	Moderate	Seve.-e
Hematology			
aPTT **prolonged**	>Ll..N - 1.5 X U...N	>1.5 - 2.5 X U...N	>2 5 x ULN; hemorrhage
Eosinophils increased•	650 - 1,500 cell/mm^3	1,501 - 5,000 cell/rrrn^3	>5 000 cell/mni3
Fibr"inogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<O.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<O 5 x LLN or ::I::50% decrease from baseline
Hemoglobin decreased **(Anemia)**	**Hemoglobin** (Hgb) <LLN- 10.0 g/dL; <LLN - 6.2 nvnol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 *mmoVL;* <100 - 80g/L	**Hgb**<8.0 g/dL; <4 9 mmoVL; <80 g/L; transfusion indicated
Hemoglobin inc,.eased	Increase in >0 - 2 g/dL abo..... e l.LNor aboYe baseline ifbaseline is abo\oe **ULN**	Increase in >2 -4 g/dL above LLN or above baseline if baseline is aboveLLN	Incr-ease in >4 g/dL above u..N or above baseline if baseline is abo'lle U...N
11\R increased	>**I** - 1.5 **XIJLN;** >1 - 1.5 times abovebaseline if on anticoagulation	>1.5 - 2.5 **X ULN;** >1.5 - 2.5 times above baseline if on anticoagt.Jation	>25xl.LN; >2 5 times above baseline if on anticoagulation
L hocyte collIt decreased	<LLN - 800/rm.3; <LLN- 0.8 x 10^9/L	<800 - 500/rr.-rl; <0.8 - 0.5 x 1o-9 /L	<500 /mm^3; <O 5 x 10^9 /L
L hocyte colrlt increased	-	>4000/rrvn^3 - 20,000/rrvn^3	>20,000/mm^3
Neutrophil coo..nt decreased	<LLN - 1500/mm^3; <LLN- 1.5 x 10^9 /L	<1500 - 1OOO/mm^3; <1.5- 1.0 x 1()^9 /L	<1000/mm^3; <1 0 x 10^9 /L
Platelet cotn: decreased	<LLN -75,000/rrvn3; <LLN-75.0 x 10^9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 X 10^9 /L
White blood cell decreased	<LLN -3000/mm^3; <LLN-3.0 x 10^9 IL	<3000 -2000/mm^3; <3.0 - 2.0 X 10^9 /L	<2000/mm^3; <2 0 X 10^9 /L
Chemistry			
Aciclosis	pH <normal, but >=7.3	-	pH <7.3
Alarine aminotransferase increased	>Ll..N - 3.0 X U..N	>3.0 - 5.0 X U..N	>5 0 x Ll..N
Alkaline phosphatase increased	>LILN -2.5 x U..N	>2.5 - 5.0 X U..N	>5 0 XI.ILN
Alkalosis	pH >normal, but :li:7.5	-	pH >7.5
Aspartate aminotransferase increased	>Ll..N - 3.0 X U..N	>3.0 - 5.0 X U..N	>5 0 x Ll..N
Blood bilirubWl increased	>LILN - 1.5 x U..N	>1.5 - 3.0 X U..N	>3 0 XI.ILN
cardiac troponin I increased	Levels above the upper limit of normal an::t below the level of myocardial ir,-arction as defined by the marufactl.rer	-	Levels consistent with myocardial infarctionas defined by the marufactlM"er
cardiac troponin T increased	Levels above the upper limit of normal an::t below the level of myocardial ir,-arction as defined by the marufactlM"er	-	Levels consistent with myocardial infarction as defined by the marufactlM"er
CPI< inc.-eased•	>U...N- <6 ULN	6-10xl1-N	>10 X ll_N
GGTIncreased	>Ll..N -2.5 X U..N	>2.5 - 5.0 X l.A..N	>5 0 XLl..N
Hyperglycemia	Fasting glucose value >LLN - 160 mg/dL; Fasting glucose value >Ll..N - 8.9 **rrrnoVL**	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmoVL	>250 mg/dL; >13.9 **mmoVL;** hospitalization indicated
Hypenricemia	>**ULN** - 10 mg/dL (0.59 mmoVL) withol.i physiologic consequences	-	>**ULN** - 10 mg/dL (0.59 rnnoVL) withphysiologic consequences
Hypoalblnlinemia	<LLN -3 g/dL; <LLN- 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypoglycemia	<LLN - 55 mg/dL; <LLN -3.0 nvnol/L	<55 mg/dL; <3.0 nvnol/L	<40 mg/dL (<2.2 rrrnol/L) At-0 requires assistance of another person to actively administer carbohydrates, glucagon, or take other COrTective actions.
Lipase increased	>U....N - 1.5 x U..N	>1.5- 2.0 x U..N	>20xU...N
Serunamylase increased	>Ll..N - 1.5 x U..N	>1.5- 2.0 X l.A..N	>20xU...N

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Hyperglycemia	Fastilg glucose value >ULN - 160 mg/dl; Fasting glucose value >ULN - 8.9 mmoVL	Fasting glucose value >160 - 250 mg/dl; Fasting glucose value>8.9- 13.9 rmiol/L	>250mgldl;>13.9 mmol/L; hospitalizationindicated
Hyperuricemia	>ULN - 10 mg/dl (0.59 mmoVL) witoout physiologic car-sequences	-	>ULN - 10 mgldl (0.59 mmol/L) with physiologic consequences
Hypoalb1mioomia	<LLN - 3 g/dl; <LLN-30g/L	<3- 2 g/dl; <30 - 20 g/L	<2g/dl; <20 g/L
Hypoglycemia	<LLN - 55 mg/dl; <LLN - 3.0 mmoVL	<55mg/dl; <30 mmoVL	<40 mg/dl (<2.2 mmoVL) All[)reqLires assistance of another personto actively admnster carbohydrates, glocagon, or take other correcti\e actions'
Lpase increased	>ULN- 1.5 x ULN	>1 5-2.0 x ULN	>2 0 x ULN
Ser1mamylase **increased**	>ULN- 1.5 x ULN	>1 5-2.0 x ULN	>2 0 x ULN

'Grading for tt-isparameter is derived from theToxicity Grading Scale for Healthy Adut and Adolescent Vollllleers E..-olled in Preventive Vaccine Clinical Trials, Sept 2007

•Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

'Modified for consistency withthe ADAand Endocrine Society GLidelines (SeaqList ER, Anderson J, Ct-ilds B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)